Gold-Catalyzed Ring Expansions of Stabilized Cyclopropyl Rings

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David Garayalde Hernandez

aus Spanien

Promotionskomitee

Prof. Dr. Cristina Nevado (Vorsitz und Leitung der Dissertation)

Prof. Dr. John Robinson

Prof. Dr. Stefan Bienz

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I cannot finish without saying how grateful I am with my family. I wish to thank my parents and my brother because they have always supported and encouraged me to do my best in all matters in life.

Finally, I would like to dedicate this thesis to the most important person in my life, Teresa, without whom this effort would have been worth nothing. Your love, support and constant patience have taught me so much all these ten years.

Foreword

This PhD thesis, except for Chapter 1, is based on the results published or going to be published in international scientific journals, Chapter 2, 3, 4 and 5 correspond to the papers in as much unchanged form of the respective manuscripts as possible. Therefore, compounds and references are number independently in each chapter.

The following publications have stemmed from this work:

1. **Gold-Catalyzed Cycloisomerization of Cyclopropyl Alkynyl Acetates: A Versatile approach to 5-, 6- and 7-membered carbocycles** Y. Zou; D. Garayalde; Q. Wang*; C. Nevado*; A. Goeke* *Angew. Chem. Int. Ed.*, **2008**, *47*, 10110-10113.

2. **Mechanistic Insights in Gold-Stabilized Nonclassical Carbocations: Gold-Catalyzed Rearrangement of 3-Cyclopropyl Propargyl Acetates** D. Garayalde; E. Gomez-Bengoa; X. Huang; A. Goeke*; C. Nevado* *J. Am. Chem. Soc.,* **2010**, *132*, 4720-4730.

3. **Gold-Catalyzed Cyclopenta- and Cycloheptannulation Cascades: A Stereocontroled Approach to the Scaffold of Frondosins A and B** D. Garayalde; K. Krüger; C. Nevado* *Angew. Chem. Int. Ed.,* **2011**, *50*, 911-915.

Zusammenfassung

Die weitgehenden Entwicklungen im Bereich der homogerner Katalyse zeigt die wichtige Rolle von Goldkatalysatoren als carbophile Lewis-Säure. Auf Grund des starken relativistischen Effekts besitzt Gold diese Koordinationseigenschaften. Sowohl Gold(I) als auch Gold(III) können ungesättigte funktionelle Gruppen aktivieren, was Zugang zu einer weiten Palette an Transformationen gibt. Abgesehen von dessen Eigenschaft als Lewis-Säure, kann Gold auch für Ringerweiterungen eingesetzt werden.

Eine ausgereifte Strategie für den Zugang hoher Struktordiversität ist die Anwendung von Propargylcarboxylaten in katalytischen Prozessen, bei denen die Carbonylgruppe als Nukleophil ein metall-aktiviertes Alkin angreift. Auf Grund des modularen Aufbaus, können verschiedene zusätzliche funktionelle Gruppe einfach eingefügt werden. Dies kann auch bei intramolekulare Reaktionen eingesetzt werden um hochgradig funktionalisierte Verbindungen zu erhalten.

Diese Doktorarbeit beschreibt neue methodologisch ausgearbeitete übergangsmetalle-katalysierte Verfahren wie Cycloisomerisierungen von δ^+ stabilisierend funktionalisierten Cyclopropylringsystemen, was neue Zugänge für die Synthese strukturell komplexen Molekülen gibt.

Im ersten Teil dieser Arbeit wird die Weiterentwicklung Gold katalysierten Cyclopropylring Erweiterung durch Alkene und Alkine beschrieben. Eine höchst effiziente Methode für die Synthese von (*Z*)-5-Alkylidene-cyclopent-1-enyl Acetaten, Cyclohexanonen und Cyclopentylketonen, beinhaltend einer neuen intramolekularen Acyl Migration zu nukleophielen Au(I)-C(sp^2) Bindungen, konnten unter milden Bedingungen entwickelt werden. Um die Natur der involvierten Zwischenprodukte zu verstehen, wurden mechanistische Studien durchgeführt. Zusammenfassend kann gesagt werden, dass die Umlagerungen kationischer Natur sind. Auf Grund des hohen Grades der Transformation der Stereoselektivität kann gesagt werden, dass goldstabilisierte nicht-klassische Carbokationen mit einer gewissen strukturellen Stabilität, involviert sind.

Im zweiten Teil, zwei hoch diastereoselektive Au-katalysierte 3-Schritt Kaskade Prozesse für die Synthese von hochgradig substituierten Fünferringe und Siebenerringe ausgehend von Propargyl Acetaten und Alkenen oder 1,4-Dienen wurden entwickelt. Die Reaktion bevorzugt die Bildung des *trans*-2,3-disubstituierte Cyclopentylacetats durch einen carbokationischen Übergangszustands, während durch die Gold katalysierte Cope Umlagerung das *cis*-2,3-disubstituierte Cyclopentylacetat gebildet wird. Die konzertierte Natur des letzten Prozesses erlaubt eine alternative formelle enantioselektive Synthese von Frondosin A und B.

Im letzten Teil dieser Arbeit wird die Anwendung von Gold als Lewis-Säure für die Aktivierung von Cyclopropylalkinen gegenüber verschiedener Nukleophielen beschrieben. Hochsubstituierte Tetrahydrocarbazole wurden nach einer Sequenz erhalten, welche einen Gold katalysierten nukleophielen Angriff des heteroaromatischen Nukleophils in der Gegenwart stabilisierten Cycloprpylring enthaltenden Alkinen. Eine tiefgehende mechanistische Studie wurde durchgeführt, um diese Transformation besser zu verstehen und hauptsächlich die Regioselektivität dieses Prozesses zu erklären.

Summary

The largest developed area in homogeneous catalysis comprises the use of gold as a carbophilic Lewis acid due to the strong relativistic effects governing its coordination behavior. Both gold(I) and gold(III) complexes are able to activate unsaturated moieties, triggering a broad palette of transformations. However, beyond its Lewis acidity, gold has also proved to be extremely powerful in triggering ring-expansion processes to introduce structural complexity into organic molecules.

A mature strategy to access a large structural diversity is the use of propargylic carboxylates in catalytic processes, where the carbonyl group acts as a nucleophile onto the metal-activated alkyne complex. Due to their easy and modular preparation, various additional functional groups can be readily incorporated to decorate the core structure and, importantly, be rendered to participate in reactions in an intramolecular manner, therefore offering highly functionalized products and increasingly diverse reaction manifolds.

The work described in this thesis is dedicated to the development of new methodologies catalyzed by late transition metals involving cycloisomerizations of cyclopropyl rings bearing groups δ^+ stabilizing that have opened new venues for the synthesis of structurally complex molecules.

In the first part of this thesis we report our investigation into the cyclopropyl ring expansion driven by Au-activation of alkynes and allenes. A highly efficient method for the synthesis of (*Z*)-5-alkylidene-cyclopent-1-enyl acetates, cyclohexenones and cylopentenyl ketones has been developed under mild conditions, featuring a novel intramolecular acyl migration to nucleophilic Au(I)-C(sp^2) bonds. Mechanistic studies have been performed in order to get a better understanding of the nature of the intermediates involved in these transformations. Although the rearrangements are cationic in nature, the high degree of stereochemical information transfer in these reactions suggests that gold-stabilized nonclassical carbocations with a certain configurational stability are involved.

In the second part, two highly diastereoselective Au-catalyzed 3-step cascade processes for the synthesis of highly substituted 5- and 7-membered rings from propargyl acetates and alkenes or 1,4-dienes, were investigated. The reaction favors *trans*-2,3-disubstituted cyclopentenylacetates through a tightly bound carbocationic transition state whereas the gold-catalyzed Cope rearrangement delivers *cis*-2,3-disubstituted cycloheptenylacetates. The concerted nature of the last process has allowed an alternative formal enantioselective synthesis of frondosins A and B.

In the last part of this thesis, we investigated on the use of gold as a Lewis acid for the activation of cyclopropylalkynes towards a variety of nucleophiles. Highly substituted tetrahydrocarbazols are obtained in a sequence that involves the gold-catalyzed nucleophilic attack of heteroaromatic nucleophiles in the presence of stabilized cyclopropyl rings bearing alkyne moieties. An in-depth

mechanistic study to better understand these transformations is also performed, particulary those aspects related to the regioselectivity of the process.

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Introduction

1.1. Introduction

1.1.1 An historical perspective

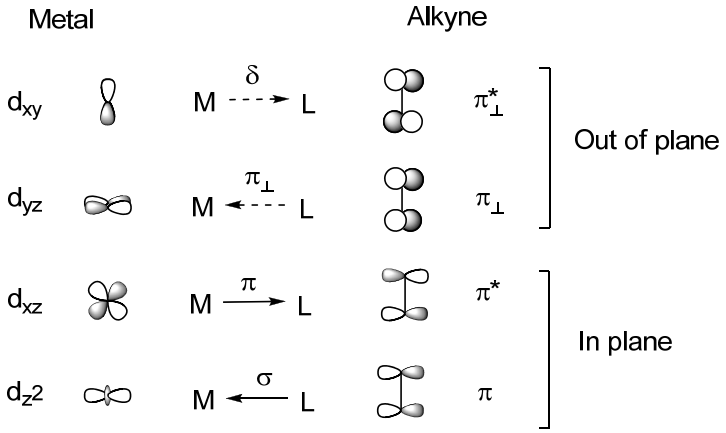
From the very early days, gold has fascinated mankind. The symbol of gold (Au) is coming from the Latin "*aurum"* and its discovery is not associated to any chemist. Alchemist were convinced metals were present in nature just as precursors of gold, as gold was consider to be the most perfect metal and nature always strives for perfection. Gold is a dense, soft, shiny, malleable and ductile metal. Pure gold has a bright yellow color and luster traditionally considered attractive, which it maintains without oxidizing in air or water. For a long time, gold was considered to possess only low catalytic activity[1] and therefore only its stoichiometric coordination and organometallic chemistry was investigated intensively. However, in the last two decades, the use of gold as catalyst in homogeneous and heterogeneous systems has grown exponentially.[2]

Nowadays, the most successful area in gold homogeneous catalysis falls into the ability of gold to coordinate and activate unsaturated moieties such as alkenes, alkynes, allenes or even arenes due to the strong relativistic effects governing its coordination chemistry.[3]

1.1.2 Basic concepts of carbophilic activation: alkynophilicity and π-acidity

The Dewar-Chatt-Duncanson (DCD) model is a qualitative model in organometallic chemistry that explains the type of chemical bonding between an alkene or alkyne and a metal (π-complex) in certain organometallic compounds.[4] The bond between the metal and the ligand is consider as a donor-acceptor interaction between the two closed-shell fragments assuming that a σ bond is formed by overlapping of the π system of the ligand (alkene or alkyne) with an empty metal orbital of suitable symmetry.[5] Two contributions in plane as well as two contributions out of plane are found in d^{10}-gold complexes (Scheme 1).

Scheme 1. Qualitative DCD diagram for a metal-alkyne bond



The in-plane interactions represent the major contributions of this bonding situation: σ-symmetric M←L donation arises from the overlapping between the π orbital of the ligand with an

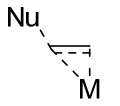
empty orbital (d_z^2) of the metal. π-Symmetric M→L back-donation occurs by donation of electron density from the filled d_{xz} orbital of the metal into an anti-bonding π^* orbital of the ligand.

On the other hand, the orthogonal, out-of-plane π orbitals can engage in M←L π donation, while mixing of an occupied d orbital of the metal and the empty π^* orbital of the ligand can result in an additional component of M→L back-donation. The DCD model predicts a partial rehybridization and an elongation of the double or triple bond as a consequence of the net shift of elelctron density from the bonding π orbital into the antibonding π^* orbital. Indeed, withdrawal of electron density from any metal that binds to an unsaturated C-C bond makes it more electrophilic and thereby can be defined as a π acid.

Minor changes in the C-C bond length between the coordinated and the free ligand are observed. In addition, the C atoms present a near linear or near trigonal coordination geometries for alkyne and alkene respectively, with low degrees of rehybridation. Due to the overall depletion of electron density, the alkyne or alkene ligand is susceptible to nucleophilic attack to form alkenyl- or alkyl metal complexes respectively. However, the mechanism of nucleophilic attack to a coordinated olefin or alkyne has been the subject of much controversy. The alkynophilicity of the gold catalyst reflects the preference of the incoming nucleophile for attack at the coordinated triple bond.

Computational studies have showed that for various model complex-ligand systems the transition state for nucleophilic addition reactions are not near the equilibrium η^2 structure. It is now accepted that the non symmetric contribution of each of the carbons of the π moiety is enhanced upon $\eta^2 \rightarrow \eta^1$ deformation (slippage), facilitating charge transfer from the nucleophile to the π ligand and finally to the metal center (Scheme 2).[6]

Scheme 2. Schematic representation of slippage



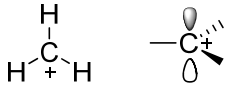
slippage

1.2. Non-Classical Carbocations: From Controversy to Convention

1.2.1 Classical carbocations

A cornerstone of the classical theory of structural chemistry since the time of Kekulè in the XIX century is that carbon can bind at most four other atoms (tetra-coordination). A carbocation (carbonium ion) is an ion with a positively-charged carbon atom. The charged carbon atom in a carbocation has only six electrons (“sextet”) in its outer valence shell instead of the eight valence electrons (“octet”). Therefore carbocations are reactive forms that are seeking to fulfill the octet of valence electrons to gain a neutral charge. Carbocations present a sp^2 hybridization with a trigonal planar geometry (Scheme 3).

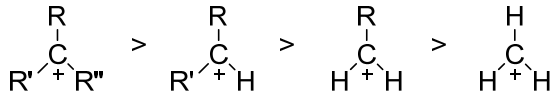
Scheme 3. Representation of a carbocation



Carbocations are intermediates in several kinds of reactions,[7] and are classified as primary, secondary and tertiary depending on the number of carbon atoms bonded to the ionized carbon. The stability order can be explained by inductive effect, which is the transmission of charge through a chain of atoms by electrostatic induction, and by hyperconjugation, which is the interaction of the electrons in a sigma bond (usually C-H or C-C) with an adjacent empty non-bonding or antibonding orbital. In the polar or inductive effect, nonconjugated substituents exert an influence on stability through bonds (inductive effect) or through space (field effect). Tertiary carbocations presents a greater polar effect that leads to great stability (Scheme 4).

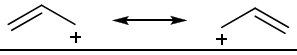
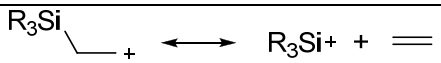
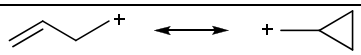
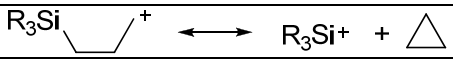
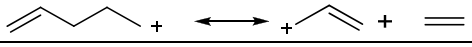
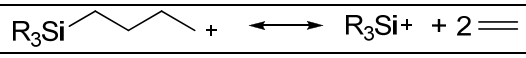
According to the hyperconjugation model, is seems that the primary ion has only two hyperconjugative forms while tertiary has six. Furthermore, the greater number of resonance forms, the greater the resonance stability.

Scheme 4. Order of stability of alkylcarbocations



There are several structural types of delocalization which have been summarized in Table 1.[8]

Table 1. Types of carbocation delocalization

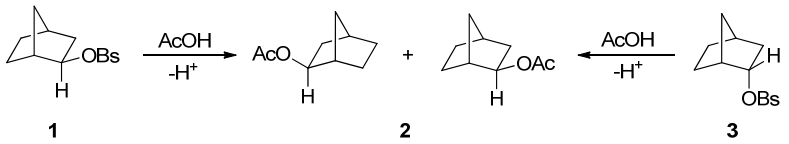
Entry	Valence structures	Shorthand	Name
1		ππ	Simple conjugation
2		σπ	Hyperconjugation
3		πσ	Homoconjugation
4		σσ	Homohyperconjugation
5		σπ/ππ	Hyperconjugation/conjugation
6		σπ/ σπ	Double hyperconjugation

In the allyl cation, the simplest and most fundamental type of delocalization is found (Table 1, entry 1). This mode is based on the fact that both donor and acceptor orbitals are π-type, and the use of simple conjugation indicates that there are no intervening saturated atoms between donor and acceptor. When the donor is a σ bond, the phenomenon is called hyperconjugation (Table 1, entry 2). The effects of hyperconjugation are greater with better sigma donors such as Si-C rather than C-H or C-C bonds.[9] The presence of a saturated atom between the donor and acceptor orbitals leads the homoconjugation (Table 1, entry 3). The orbital overlap is a mix of σ and π contributions due to the non-parallel relationship between each other.[10] When a saturated center intervenes between a σ donor and the carbocationic acceptor, the phenomenon is called homohyperconjugation (Table 1, entry 4). This mode of delocalization is considered to be primarily direct and through space. In the hyperconjugation/conjugation mode of delocalization (Table 1, entry 5), the positive charge moves into the σ system through hyperconjugation and then into the π system through simple conjugation. The last entry in Table 1 ilustrates the concept of double hyperconjugation as two stages of hyperconjugation to bring the effect of the donor element to the empty π orbital.[11]

1.2.2 Non-classical carbocations

Non-classical cations in organic chemistry are a special type of carbonium ions displaying delocalization of sigma bonds in 3-center-2-electron bonds of bridged systems. Around 1950, Winstein and Trifan found a short-lived carbocation that contained a penta-coordinated carbon atom. They observed that the solvolysis reaction in acetic acid of optically active *exo*-2-norbornyl brosylate **1** gave racemic mixtures of the two *exo* acetates **2** (Scheme 5).[12]

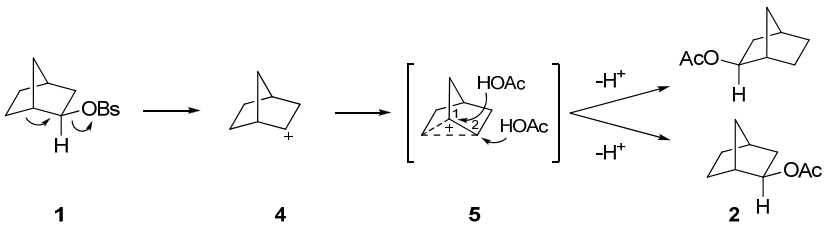
Scheme 5. Solvolysis of *exo*- and *endo*-2-nobornyl brosylates



Furthermore, the *exo*-2-norbornyl brosylate **1** solvolyzed around 350 times faster that its *endo* isomer **3**. These results were interpreted by means of the nonclassical intermediate **4**, which was involved in the departure of the leaving group. Due to the non favorable position for backside attack, solvolysis of the *endo* isomer **3** takes place at normal rate compared to the *exo* isomer **1**. Therefore the much faster rate for the solvolysis of **1** must be caused by anchimeric assistance of the neighboring σ bond.

The stereochemical outcome of the reaction was explained by the intermediacy of **5**. In this intermediate, positions 1 and 2 are equivalent and would be equally attacked by the nucleophile only from the *exo* direction (Scheme 6).

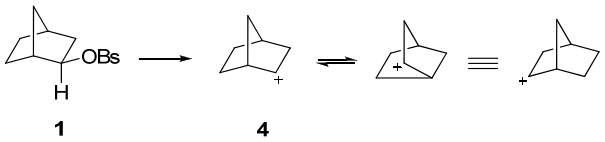
Scheme 6. Wistein's postulate



Winstein postulate that a classical ion **4** is formed after the release of the leaving group in **1** and then converted into the more stable carbocation **5**.

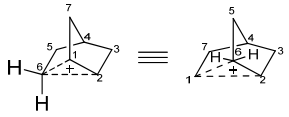
This pioneering and controversial discovery initiated a vigorous academic dispute. The concepts of σ participation and the nonclassical ion **5** were challenged by H. C. Brown.[13] He concluded that the norbornyl cation was a tri-coordinated cation (carbenium ion) that rapidly rearranged into an identical tri-coordinated ion in which the positive charge had moved to another carbon atom in a rapid equilibrium (Scheme 7).[14]

Scheme 7. Brown's hypothesis



Despite great efforts by many leading physical organic chemists, the problem remained unsolved until Olah's method of preparing long-lived carbocations was applied.[15] This method consisted in the preparation of stable carbocations using a new type of extremely acid compounds (superacids) as solvent at low temperatures. Olah and coworkers represented the nonclassical structure as a corner-protonated nortricyclane **6**, whose symmetry is better seen in **7** (Scheme 8).

Scheme 8. Olah's representation of nonclassical cation



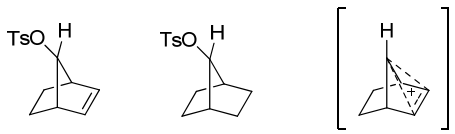
6 **7**

In these structures, almost all the positive electron density resides on C-1 and C-2 and few on the bridging carbon C-6. Other evidence for the nonclassical nature of 2-norbornyl cation comes from the experiment that show that the 2-norbornyl cation is more stable (6-10 Kcal/mol) than would be expected without the bridging.[16] Infrared spectra experiments of the 2-norbornyl cation in gas phase also point towards a nonclassical structure.[17] *Ab initio* calculations have showed that the nonclassical structure corresponds to an energy minimum.[18]

1.2.3 Other important non-classical carbocations

The participation of a C=C double bond as a neighboring group represents another class of nonclassical carbocation. In this context, the most striking evidence that the C=C double bond acts as a neighboring group is the fact that the acetolysis of **8** is 10^{11} times faster than that of **9** and proceeds *via* retention of the configuration.[19] The rate of acetolysis of **8** involves the formation of a nonclassical intermediate **10**, with the strong evidence that the C=C group assists the departure of the OTs group. In this system, the double bond is geometrically fixed in a favorable position for backside attack on the carbon bearing the leaving group (Scheme 9).

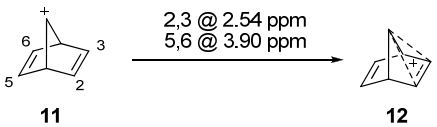
Scheme 9. C=C bond as neighboring group



8 **9** **10**

^{1}H-NMR studies of norbornadienyl model system **11** proved the nonequivalence of the protons bonded to the alkenylic carbons 2,3 and 5,6 in the norbornenyl cation **12**. Thus, an evidence for the existence of this nonclassical carbocation **12** is that there is interaction between the charged carbon atom and one double bond (Scheme 10).[20]

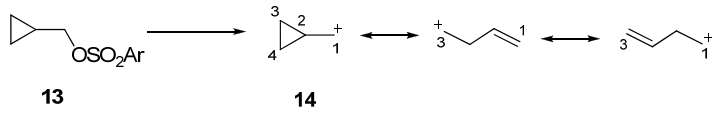
Scheme 10. Norbornenyl cation model



11 **12**

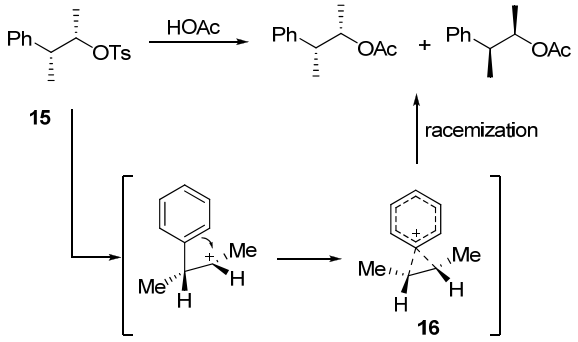
Apart from the 2-norbornyl case, the cyclopropylmethyl system represents another important class of this special type of carbocations. Cyclopropylcarbinyl benzenesulfonates **13** solvolyze with high rates and the products include unrearranged cyclopropylmethyl as well as cyclobutyl and homoallylic compounds. In these systems, the participation of the σ bonds of the ring enhances the rate of solvolysis of simple primary cyclopropylmethyl substrates. In the symmetrically stabilized cation **14** formed in the reaction, both the 2,3 and 2,4 σ bonds help the stabilization of the generated positive charge (Scheme 11).[21]

Scheme 11. Cyclopropylmethyl cation system



Phenonium ion is another important figure in the context of nonclassical carbocations. There is a great deal of evidence that aromatic rings in the β position of a leaving group can act as neighboring groups.[22] Solvolysis rates of *L-threo*-3-phenyl-2-butyl tosylate **15** in acetic acid have been extensively studied.[23] The aryl group behaves as neighboring group pushing out the leaving group to give the bridged ion **16** (*phenonium ion)*. The stereochemical outcome of this reaction is an evidence of the formation of these type of intermediates (Scheme 12). The solvolysis reaction of **15** afforded 96% of the *threo* isomer and only about 4% of the *erythro*. Moreover, both the (+) and (-) *threo* isomers were produced in approximately equal amounts. When the reaction is conducted in formic acid, even less *erythro* isomer was obtained. This result leads to the conclusion that configuration is retained because phenyl group acts as neighboring group.

Scheme 12. Solvolysis of *L-threo*-3-phenyl-2-butyl tosylate **15**

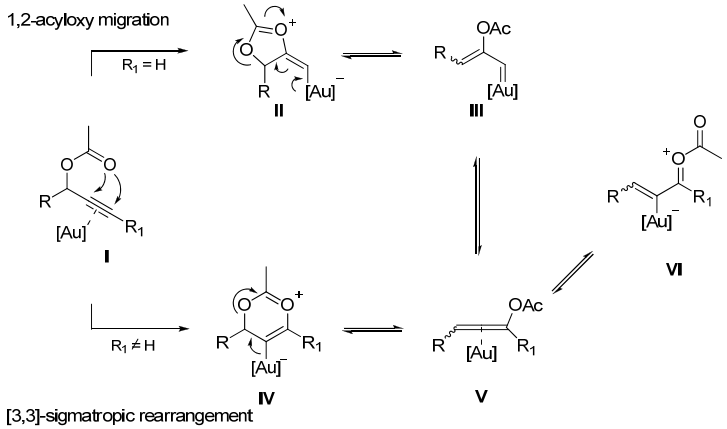


1.3. Rearrangement of Propargyl Carboxylates

1.3.1 General considerations

Homogeneous gold catalysis is currently undergoing an impressive renaissance centered on alkyne activation and subsequent functionalization.[24] A growing area of research concerns the use of propargylic carboxylates in catalytic processes. The nature of such substrates is complementary to the pull-push reactivity of metal-activated alkynes. Upon coordination to the alkyne, gold can effiently activate propargyl carboxylates (**I**) towards two competitive processes that seem to be mechanistically related: 1,2-acyloxy migration and/or [3,3]-sigmatropic rearrangement (Scheme 13).[25]

Scheme 13. 1,2-acyloxy migration vs. [3,3]-sigmatropic rearrangement

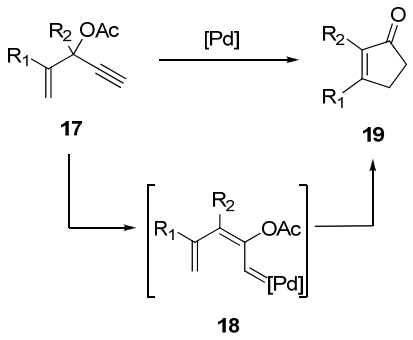


Notably, the propensity of these easily accessible compounds to undergo a migration of the carbonyloxy group leads to the formation of a gold vinyl carbenoid species **III** *via* 1,2-migration of the acetyl moiety in which both the ester and the π system have migrated from their original positions whereas allenyl acetates **V** are formed *via* [3,3]-sigmatropic rearrangement. Allenyl acetates **V** can be formed in a single process or stepwise by a second acetate migration from the corresponding carbene intermediate **III**.[26] In presence of the gold catalysts, allenyl species **V** can be further activated opening a broad palette of chemical transformations. Substitution patterns on the propargyl moiety play an essential role in dictating the reaction pathway. It is widely accepted that terminal or electron-poor alkynes react *via* 1,2-acyloxy migration,[27] whereas internal alkynes prefer the 1,3-migration pathway.[28]

1.3.2 1,2-Acyloxy migration

In 1976, Günter Ohloff reported the first example of a rearrangement of propargyl acetates mediated by stoichiometric amounts of Zn-salts.[29] Ten years later, Valentin Rautenstrauch, reported a related Pd-catalyzed cyclization of 1-ethynyl-2-propenyl acetates **17** to give cyclopentanones **19** postulating the formation of a Pd-carbene intermediate **18** (Scheme 14).[30]

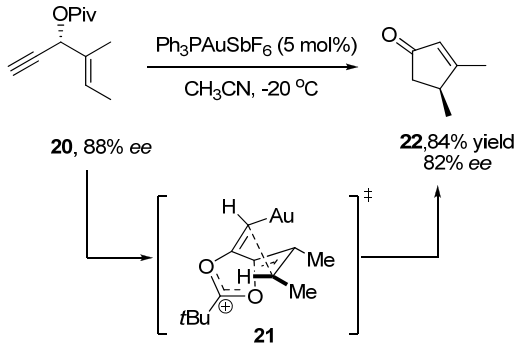
Scheme 14. Rautenstrauch cyclization



Twenty years later, Toste and coworkers revisited this chemistry using enantiomerically pure propargyl acetates and gold(I) complexes.[31] These authors observed that the stereochemical information in the propargyl position of the starting material **20** was transferred into the final

product **22**. The high degree of enantioselectivity observed in these rearrangements suggests that a mechanism involving C-C bond formation prior to scission of the stereogenic C-O bond is operating (Scheme 15). DFT calculations suggest that this reaction would be classified as the intramolecular attack of an enol acetate (with some additional charge donation from the gold complex) to an allyl cation, involving the imprint of the chiral information of the original stereocenter in the helical conformation of a pentadienyl cation **21**.[32]

Scheme 15. Toste's synthesis of substituted cyclopentenones **22**

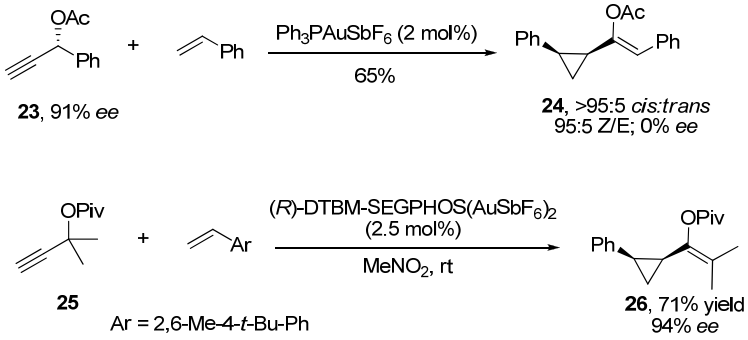


Indirect proof for the intermediacy of a carbene intermediate **III** was provided by its interception in presence of different reagents as shown in the following sections.

1.3.2.1 1,2-Acyloxy migration and olefin cyclopropanation

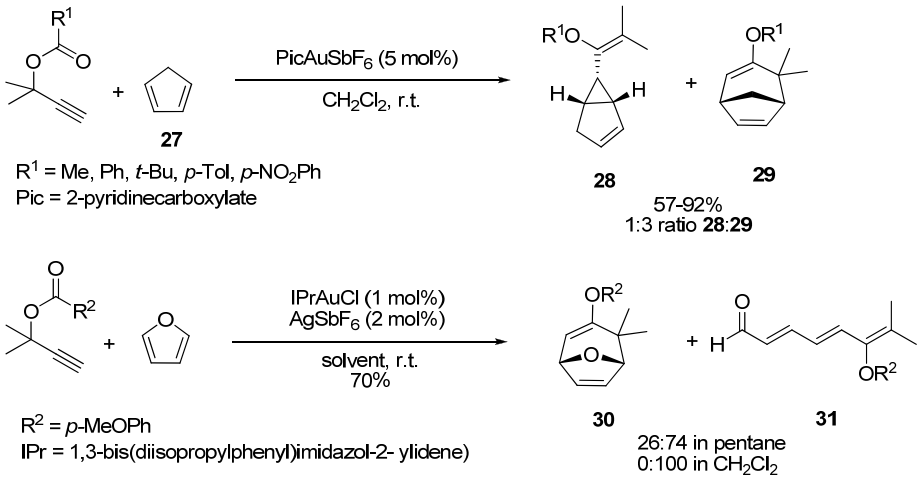
One of the first transformations providing evidence of the implication of gold carbenes in the gold-catalyzed rearrangement of propargyl acetates is shown in Scheme 16. The gold-carbene reacts with monosubstituted olefins to afford vinylcyclopropanes such as **24** and **26**.[33] The intermediacy of a planar intermediate formed in the reaction is supported by the use of enantiomerically enriched propargyl carboxylates **23**. As expected, a lack of configuration transfer affords racemic products **24**. However, good levels of asymmetric inductions can be reached when using chiral cationic gold complexes with racemic propargyl pivaloates **25** in the synthesis of cyclopropyl pivaloate **26** (Scheme 16).[34] Moreover, similar reactivity was observed in reactions of vinyl esters and vinyl sulfonamides with terminal propargyl esters for the synthesis of highly substituted cyclopropane derivates.[35]

Scheme 16. Olefin cyclopropanation



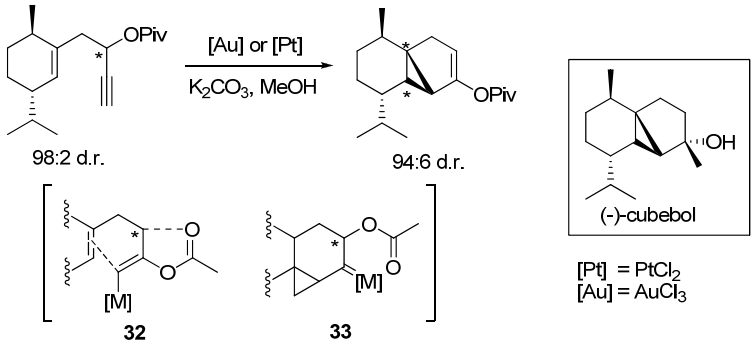
Replacing the olefin with cyclopentadiene rings **27** resulted in the formation of mixtures of vinylcyclopropanes **28** and cycloheptadienyl acetates **29** (Scheme 17).[36] A mechanism that involves a gold-catalyzed 1,2-acyloxy migration followed by an intermolecular [4+3] cycloaddition is proposed. Vinylcyclopropanes **28** can be converted into the corresponding cycloheptadienyl acetates **29** through a Cope rearrangement by heating the solution in toluene for 12 hours. The use of furan as a diene counterpart affords the formation of the corresponding 7-membered ring **30** and the triene aldehydes **31**. The same reactivity has been demonstrated in the presence of ruthenium catalysts.[37]

Scheme 17. Cyclopentadiene and furan cyclopropanation of propargyl esters



Independently, Fürstner[38] and Fehr[39] demonstrated earlier on the synthetic potential of propargyl acetate rearrangements in the stereocontrolled synthesis of (-)-cubebol and related products *via* 1,2-acetoxy migration followed by intramolecular cyclopropanation (Scheme 18). Two possible mechanistic pathways were proposed to justify the experimental results: either the olefin reacts before the acetoxy migration *via* vinyl gold species **32**, or alternatively the nucleophilic attack of the olefin takes place prior the migration of the ester moiety leading cyclopropyl carbenes type **33**. Thus, either **32** or **33** could justify the observed stereochemical configuration transfer in the above-mentioned process.

Scheme 18. (-)-Cubebol synthesis

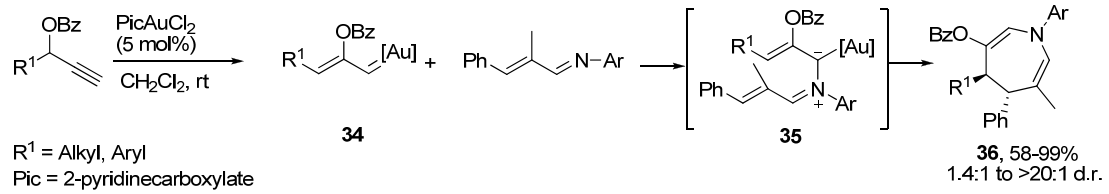


1.3.2.2 1,2-Acyloxymigration and annulations

A rapidly developing area involves the use of gold intermediates generated from 1,2-rearrangement of propargyl esters with a huge palette of dipolarophiles in a intermolecular fasion. In these reactions, the gold intermediate showed analogous reactivity to that reported for electrophilic metal-stabilized vinylcarbenoids.[40]

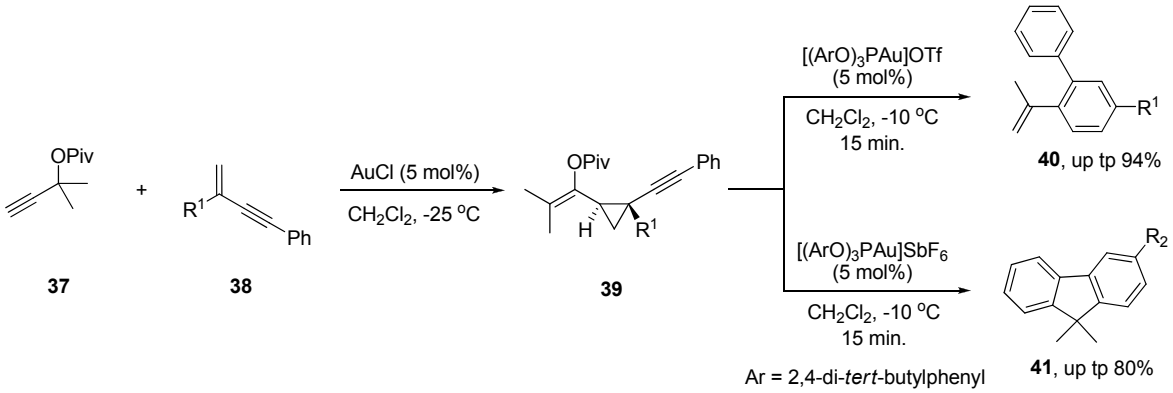
Based on this concept, the group of Toste has developed a gold(III)-catalyzed tandem process that involves 1,2-acyloxy migration/intermolecular [4+3] annulation for the straightforward synthesis of azepines **36**.[41] The authors envisioned, in analogy to related reactions of rhodium-stabilized vinylcarbenoids, that the generation of zwitterionic intermediates **35** could be accomplished by the reaction of gold-carbene **34** with a nucleophilic diene, such as an α,β-unsaturated imine. A proposed mechanism that accounts for the observed diastereoselective is proposed. Gold-promoted isomerization of the propargyl ester leads to gold-carbenoid intermediate **34**. Subsequent nucleophilic addition of the imine nitrogen generates the allylgold intermediate **35** that undergoes intramolecular nucleophilic addition onto the pendant iminium electrophile (Scheme 19).

Scheme 19. Gold-catalyzed synthesis of azepines **36**



Polysubstituted benzenes can be selectively obtained under catalysis control *via* [2+2+2] cyclotrimerization of alkynes[42] or through metal-catalyzed [4+2] cycloaddition of enynes and activated alkynes.[43] Additionally, readily available enynes **38** and propargyl esters **37** can be selectively transformed into styrenes **40** and fluorenes **41** through a gold-catalyzed intermolecular annulation processes by choice of the appropriate reaction conditions (Scheme 20).[44]

Scheme 20. Gold-catalyzed synthesis of styrenes **40** and fluorenes **41**

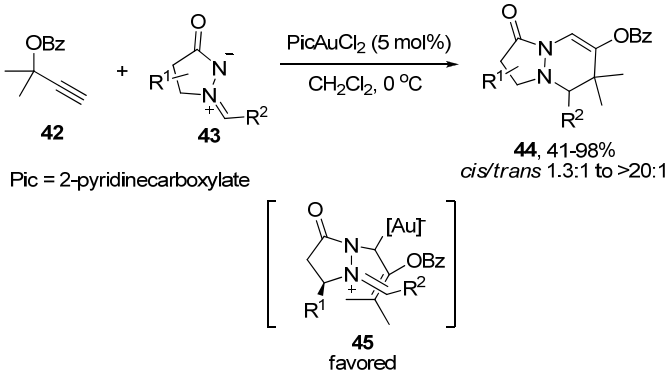


The mechanistic rationale proposed by the authors involves first, a highly diastereoselective cyclopropanation between the propargyl ester **37** and enyne **38** for the formation of the *cis*-1-vinyl-2-alkynylcyclopropanes **39**. Subsequent coordination of the gold

catalyst onto the gold-activated alkyne in **39** triggers the cyclopropyl ring opening affording styrenes **40** and fluorenes **41** in good yields. The outcome of this transformation was controlled simply through the choice of the catalyst counteranion.

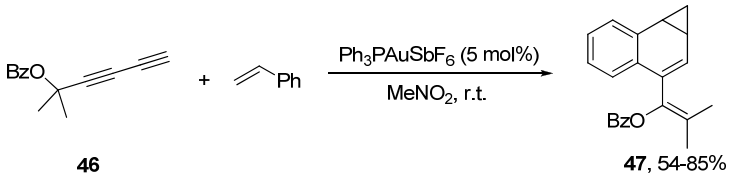
The first example of a formal [3+3] cycloaddition reaction between a gold carbenoid derived from propargyl esters **42** and azomethine imine **43** was reported in 2009 for the synthesis of diazabicycles **44** (Scheme 21).[45] The *cis* selectivity observed for these transformations can be explained by steric interactions between the methyl groups of the propargyl ester and the β-substituent in the ring closing transition state **45**. This process highlights the differences in the reactivity of alkenyl Fischer carbenes and the alkenyl gold-carbenoids generated *in situ* from the rearrangement of propargyl esters. The reaction of alkenyl Fischer carbenes with 1,3-dipoles typically proceeds via concerted [3+2] cycloaddition whereas alkenyl gold-carbenoids undergo the above mentioned [3+3] cycloaddition.

Scheme 21. Gold-catalyzed [3+3] cycloaddition between propargyl esters **42** and azomethine imines **43**



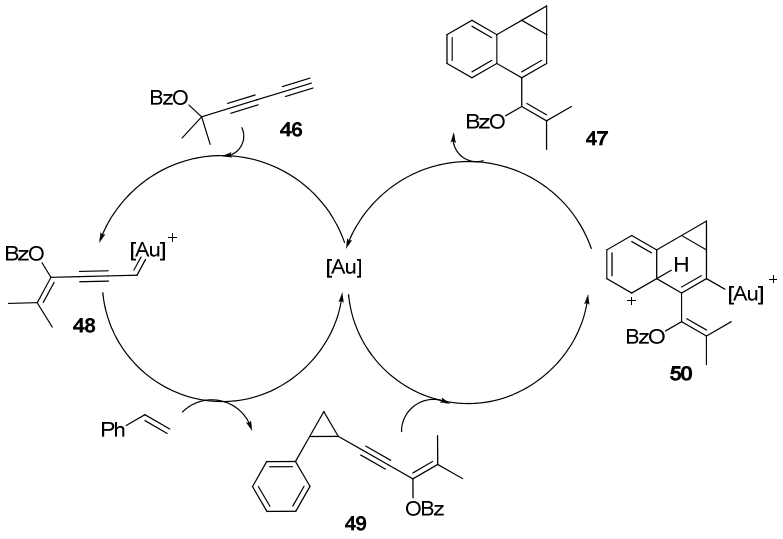
Propargyl esters-containing diynes have been employed in a number of rearrangement reactions,[46] including the formation of cyclopropanes by an intramolecular cycloisomerization.[27c] In contrast, intermolecular cyclopropanations were not observed even in the presence of excess of olefin.[27a] Cationic phosphinegold(I) complexes catalyzed a tandem cyclopropanation/ hydroarylation process with propargyl ester-containing diynes **46** and styrenes for the synthesis of substituted benzonorcaradienes **47** (Scheme 22).[47]

Scheme 22. Gold-catalyzed tandem cyclopropanation/hydroarylation



A mechanistic hypothesis is proposed for this transformation involving sequential rearrangements that proceed *via* gold(I)-promoted alkyne activation (Scheme 23). 1,2-Acyloxy rearrangement followed by 1,3-metallotropic rearrangement delivers the formation of intermediate **48**. Cyclopropanation of styrene occurs selectively through carbenoid **48**, affording intermediate **49** and regeneration of the catalyst. Subsequent gold-coordination to the alkyne in **49** induces the nucleophilic attack by the arene onto the gold-activated alkyne complex leading to the formation of intermediate **50**, which furnishes bezonorcaradiene **47** *via* proton transfer.

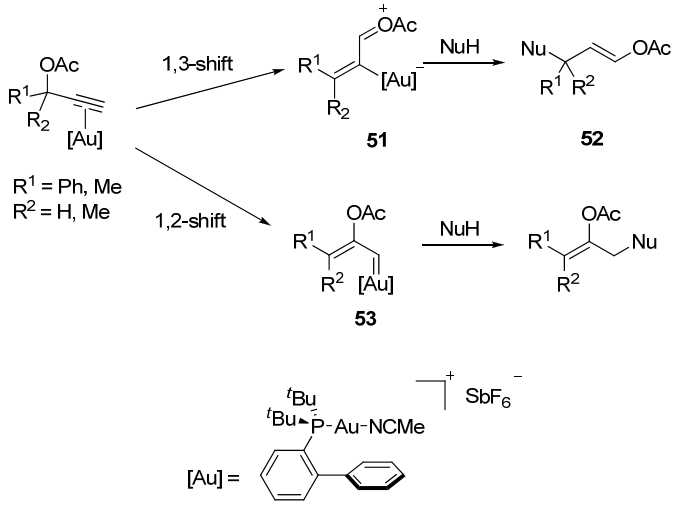
Scheme 23. Mechanistic proposal for the gold-catalyzed tandem cyclopropanation/hydroarylation



1.3.2.3 1,2-Acyloxymigration and attack by nucleophiles

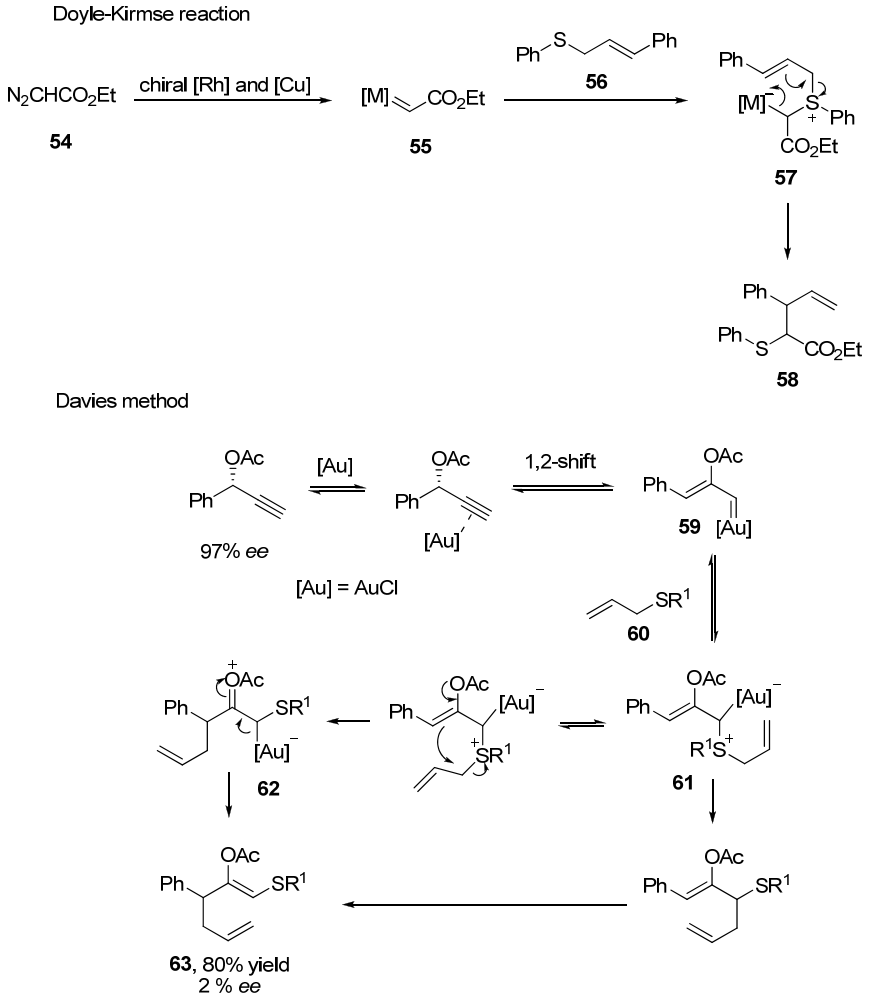
To further examine the nature of the gold-carbenoid intermediates, one should explore their reactivity with reagents previously described to be reactive toward metal carbenes. In this context, an atom-economical functionalization of carbon nucleophiles under catalytic conditions using propargyl carboxylates has been reported by Echavarren.[48] Propargyl carboxylates react with 1,3-dicarbonyl compounds and electron-rich arenes as nucleophiles in the presence of gold(I) catalysts to give enol carboxylates *via* α,β-unsaturated gold(I) carbenes formed by 1,2-acyl migration (Scheme 24). Although the factors that control the regioselectivity of the nucleophilic addition are still not totally understood, the authors observed that substrates bearing phenyl or *gem*-dimethyl groups at the propargyl position led to 1,2-addition products through α,β-unsaturated gold(I) carbenes **53**, whereas secondary propargyl acetates bearing a methyl group at the propargyl position or propargyl acetates with no substituents gave adducts **52** as a result of a 1,3-acyl migration *via* intermediates **51**.

Scheme 24. Gold-catalyzed nucleophilic attack of 1,3-dicarbonyl and arenes onto gold-activated propargyl acetates



The transition-metal-catalyzed decomposition of diazo compounds is a well established strategy to access metal carbenoids. The Doyle-Kirmse reaction is a powerful tool to generate new C-C and C-S bonds using diazo compounds with Rh(II) and Cu(I) catalysts (Scheme 25).[49] In this process, an allylsulfide **56** reacts with the metal carbenoid **55** derived from ethyl diazoacetate **54** to give a sulfur ylide intermediate **57** that is capable to undergo a [2,3]-sigmatropic rearrangement to deliver **58**. However, in this context, the group of Davies[50] reported a method that demonstrates that gold carbenoids derived from propargylic carboxylates can show a complementary mode of reactivity to carbenoids derived from the above mentioned α-diazo carbonyl compounds.

Scheme 25.Comparation between Doyle-Kirmse reaction and Davies method.

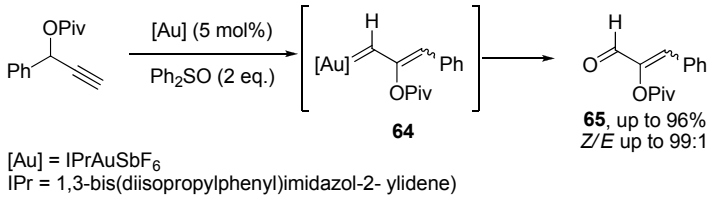


Davies proposed the generation of a ylide **61**, which can be explained *via* gold-catalyzed 1,2-acyl rearrangement followed by the nucleophilic attack of the allyl sulfide **60** onto the gold carbene **59**. The subsequent evolution of **61** into the final products proceeds through one of two pathways: a 1,2-shift or a [2,3]-sigmatropic rearrangement of the allyl fragment. An absence of chirality transfer was demonstrated in the reaction of enantioenriched starting materials, thus suggesting the intermediacy of achiral species **59**.

Toste and coworkers have been able to intercept the putative carbene intermediates generated after pivaloate migration in propargyl pivaloates by oxidation with diphenyl sulfoxide to give the aldehydes **65**. The gold carbenoid **64** that could be generated through gold(I)-induced

1,2-acyl rearrangement, can be trapped in the presence of an external oxidant, which undergoes intermolecular oxygen atom transfer to afford the aldehydes **65** with good selectivity in favor of the *Z*-olefin isomer (Scheme 26).

Scheme 26. Gold-catalyzed synthesis of aldehydes **65** with diphenyl sulfoxide



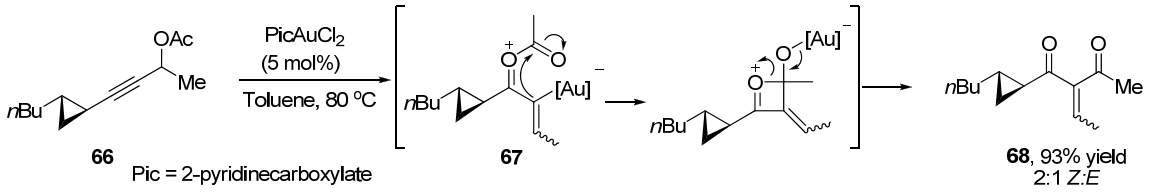
[Au] = $IPrAuSbF_6$
IPr = 1,3-bis(diisopropylphenyl)imidazol-2- ylidene)

1.3.3 1,3-Acyloxy Migration

As it was shown in Scheme 12, when internal alkynes are used, a 1,3-migration of the ester moiety is generally observed. However, DFT calculations developed by Cavallo[26] suggests that a net 3,3-rearrangement may be the result of two competitive 1,2-acyloxy migrations. Whilst the 1,2-acyl migration results in a variety of useful transformations, the corresponding 1,3-migration of propargyl carboxylates also provide valuable opportunities in a preparative context. The lack of chemoselectivity observed for cationic gold catalysts generates significant limitations for this transformation: (a) the gold-catalyzed 3,3-sigmatropic rearrangement was not considered as a practical approach for allene synthesis due to the good reactivity of the gold-activated allenes; (b) the rapid equilibrium between alkyne and allene under the reaction conditions caused poor stereoselectivity due to the rapid racemization of the propargyl stereocenter.

In absence of nucleophiles, the in situ generated allenyl acetate reacts with the gold catalyst affording vinyl-gold intermediates type **VI** (Scheme 13). Different types of reactivity can be observed for this intermediate depending on the substrate used in the transformation. Zhang and coworkers developed a highly efficient method for the synthesis of α-ylidene-β-diketones **68** *via* gold(III)-catalyzed [3,3]-sigmatropic rearrangement of propargyl esters **66** (Scheme 27).[51] They observed that, after [3,3]-sigmatropic rearrangement, intermediate **67** underwent to an intramolecular 1,2-acyl migration to the nucleophilic Au^{III}-C(sp^2) bond, affording α-ylidene-β-diketones **68** in excellent yields and moderate *Z/E* selectivities.

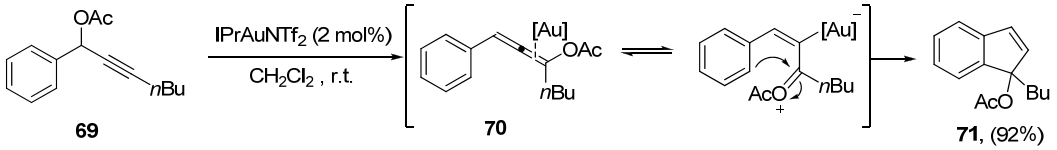
Scheme 27. Synthesis of α-ylidene-β-diketones



Pic = 2-pyridinecarboxylate

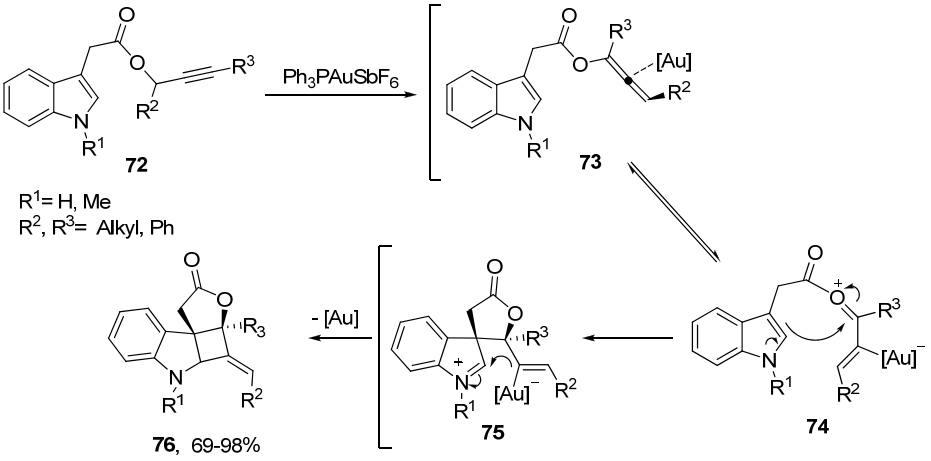
Another example that involves the reactivation of an allenyl acetate to give a vinyl gold intermediate is shown in Scheme 28.[52] The allenyl acetate **70** is formed by 1,3-migration of the acetoxy moiety in **69**. Reactivation of **70** by the gold catalyst triggers the nucleophilic attack of the aromatic ring affording the indene **71** in excellent yield.

Scheme 28. Gold-catalyzed synthesis of indenes **71**



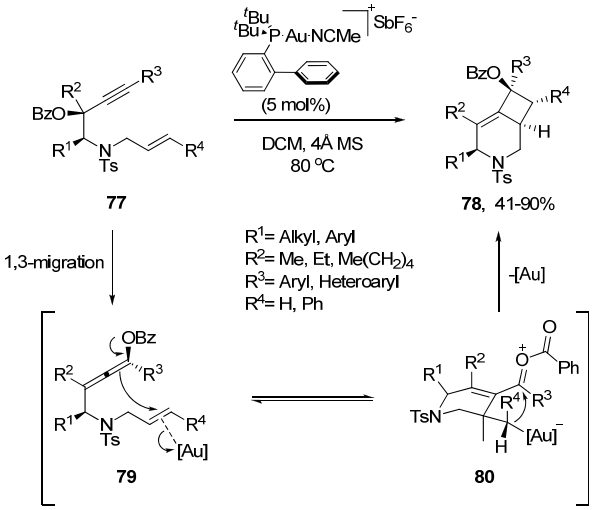
Cyclobutanes are useful building blocks in organic synthesis.[53] A powerful tool to access these structures is a tandem gold-catalyzed [3,3]-acyloxy rearrangement followed by [2+2] cycloaddition as reported by Zhang.[54] Highly functionalized 2,3-indoline-fused cyclobutanes **76** were obtained through a 1,3-migration of the acyloxy moiety in **72** delivering the allenic ester intermediate **73** (Scheme 29). Further activation of the allene moiety in **73** resulted in the formation of the thermodynamically more favored *E*-oxonium cation **74**. The formation of the cyclobutane product **76** can be explained through a [2+2] cycloaddition reaction *via* 1,4-zwitterionic intermediate **75**.

Scheme 29. Gold-catalyzed synthesis of 2,3-indoline-fused cyclobutanes **76**



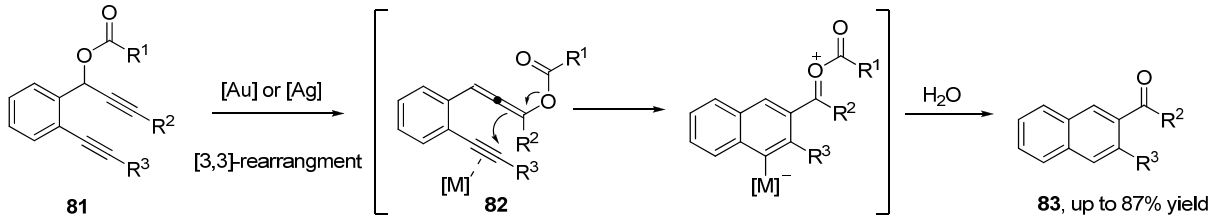
Recently, the group of Chan reported the use of propargyl benzoates **77** for the synthesis of highly substituted azabicyclo[4.2.0]oct-5-enes **78** (Scheme 30).[55] After the well-known [3,3]-sigmatropic rearrangement of the propargyl benzoate moiety in **77**, allene **79** is formed. Due to steric interactions, the gold catalyst selectively coordinates to the alkene triggering a stepwise [2+2] cycloaddition that involves the *anti* addition of the allenic group onto the gold-activated alkene affording intermediate **80**. Finally, the corresponding azabicyclo[4.2.0]oct-5-ene **78** is formed by the nucleophilic attack of the Au-C(sp^3) bond onto the carbonyl group in **80**.

Scheme 30. Gold-catalyzed synthesis of azabicyclo[4.2.0]oct-5-enes **78**



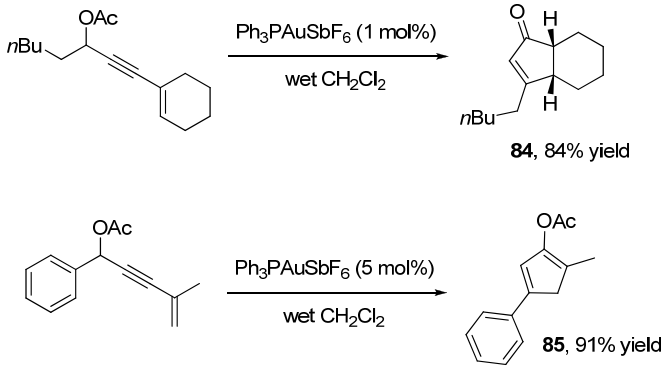
The group of Toste and Oh reported simultaneously the synthesis of aromatic ketones **83** from alkyne-propargyl acetates **81**. [56] A gold- or silver-catalyzed [3,3]-sigmatropic rearrangement followed by a Myers-Saito type cyclization[57] of the allenoate intermediate **82** is proposed by the authors for the synthesis of the naphthyl ketones **83** in a highly efficient manner. (Scheme 31).

Scheme 31. Intramolecular gold-catalyzed cyclization of alkyne-propargyl acetates **76**



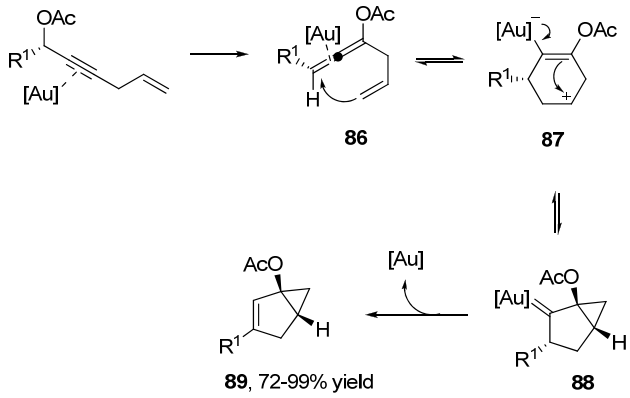
Structural features at the acetylenic position in the starting materials are also crucial for the outcome of the reaction of internal propargyl acetates in the presence of gold. When enynes are used as substrates, a Nazarov-type cyclization was observed, leading cyclopentanones **84** and cyclopentadienylic esters **85** (Scheme 32).[58] In contrast to conventional Nazarov reactions where the control of the cyclopentenone double bond is not easy, the regioselectivity of these transformations is a remarkable feature. Computational studies have revealed that the reaction of enynyl acetates was found to be faster in wet CH_2Cl_2 compared to the reaction under exhaustive dry conditions.[59]

Scheme 32. Gold-catalyzed Nazarov cyclizations



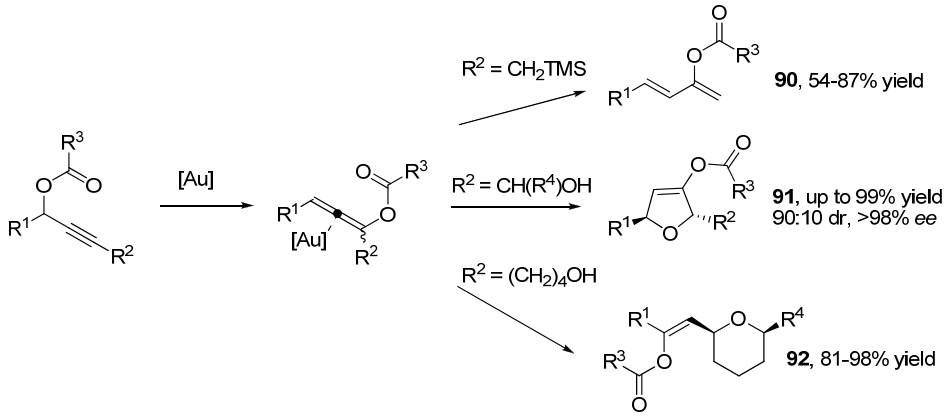
On the other hand, when a vinyl group is bound to the acetylenic position of the propargyl acetate substrate, bicycle[3.1.0]hexenes **89** were obtained in the presence of gold catalysts (Scheme 33).[60] After the initial gold-catalyzed 3,3-rearrangement of the acetate moiety, gold-reactivation of the distal double bond in the carboxyallene intermediate **86** leads to the nucleophilic attack of the vinyl group affording vinyl-gold species **87**. The cyclopropyl ring can be formed by back-donation of electron density from the gold catalyst onto the double bond. A final 1,2-hydride shift regenerates the gold catalyst and produces bicycle[3.1.0]hexanes **89** in excellent yields.

Scheme 33. Gold-catalyzed synthesis of bicycle[3.1.0]hexane **89**



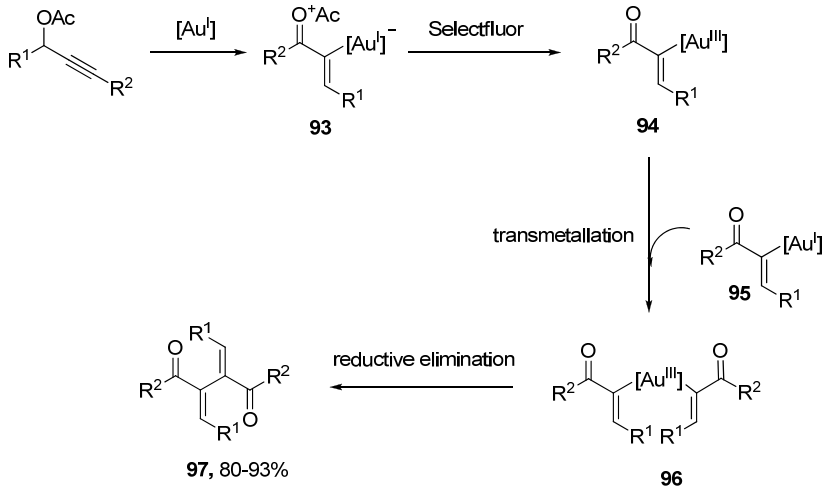
Further modifications of the substitution pattern of the alkyne allowed the synthesis of conjugated dienes **90** by gold-catalyzed protodesilylation of intermediate **V** (Scheme 13),[61] formation of dihydrofurans **91** from propargyl alcohols[62] and highly substituted tetrahydropyrans **92** by cycloetherification of ω-hydroxy propargyl esters[63] (Scheme 34).

Scheme 34. Synthesis of conjugated dienes **90**, dihydrofurans **91** and tetrahydropyrans **92**



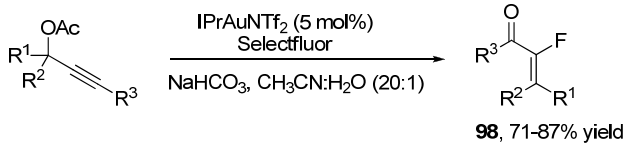
In the last years, gold-catalyzed homogeneous reactions involving gold(I)/gold(III) redox catalytic cycles represents a growing area in the context of organic synthesis. Zhang and coworkers[64] have developed a gold-catalyzed oxidative homocoupling reaction of propargyl acetates using external oxidants. The process involves a gold(I)-catalyzed [3,3]-sigmatropic rearrangement of the propargyl acetate to deliver the intermediate **93**, which is oxidized in presence of Selectfluor to form gold(III) intermediate **94**. Transmetallation with a molecule of **95** delivers the gold(III)-intermediate **96** affording the homo-coupling products **97** by reductive elimination and regeneration of the catalyst (Scheme 35).

Scheme 35. Gold(I)/gold(III) redox process for the synthesis of homocoupling products **90**



Our research group[65] expanded the scope of this chemistry. We found that, instead of the phosphine based-gold catalyst used in Zhang's approach, the use of a bulky *N*-heterocyclic ligand such as 1,3-bis(2,6-diiso-propylphenyl)-imidazol-2-ylide, afforded selectively the fluorinated products **98** (Scheme 36).

Scheme 36. Nevado's modification for the synthesis of fluorinated enones **98**

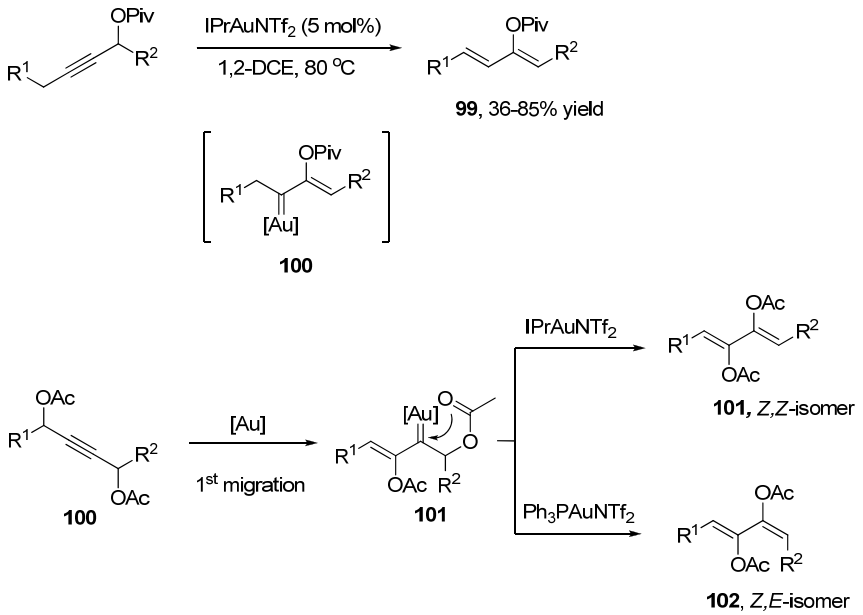


1.3.4 Exceptions to the 1,2- vs. 1,3-acyloxy migration pathways

The interconnection between the two mechanistic pathways shown in Scheme 13 for the gold-catalyzed rearrangement of propargyl acetates is an issue that has been computationally studied.[26] The reaction outcome can be influenced by sterics and electronics factors in the substituents of the starting materials.

The group of Zhang[66] has reported the use of propargylic pivalates with electronically unbiased internal alkynes for the selective synthesis of (1*Z*,3*E*)-2-pivaloxy-1,3-dienes **99**. The exceptional nature of this transformation stems from the fact that despite using internal propargyl acetates, which preferably undergo [3,3]-sigmatropic rearrangement, the reaction products can be explained by a gold carbene intermediate **100** (Scheme 37). In this process, bulky migrating groups as well as bulky catalysts are the key for the reaction success. In our research group,[67] we have developed a new gold-catalyzed tandem 1,2/1,2-bisacetoxy rearrangement of 1,4-bis-propargyl acetates **101**, which provides access to 2,3-bisacetoxy-1,3-dienes **103** and **104** (Scheme 37). Although that 1,4-diacetoxy-alkynes should react via 1,3-acyl migration, the formation of these products can be explained *via* gold-carbene **102**, which is formed by a first 1,2-rearrangement of the acetate in **101**. Based on experimental and computational studies we demonstrated that the stereochemistry of the double bond, after the first acetoxy migration, in the final product is controlled by the ligand of the catalyst. The second migration of the ester moiety always seems to be selective to the *Z* isomer. Propargyl esters with lower stabilization in the propargyl position showed a reaction selectivity influenced by the order of the migrating groups.

Scheme 37. 1,2- vs. 1,3-acyloxy migration. Exceptions



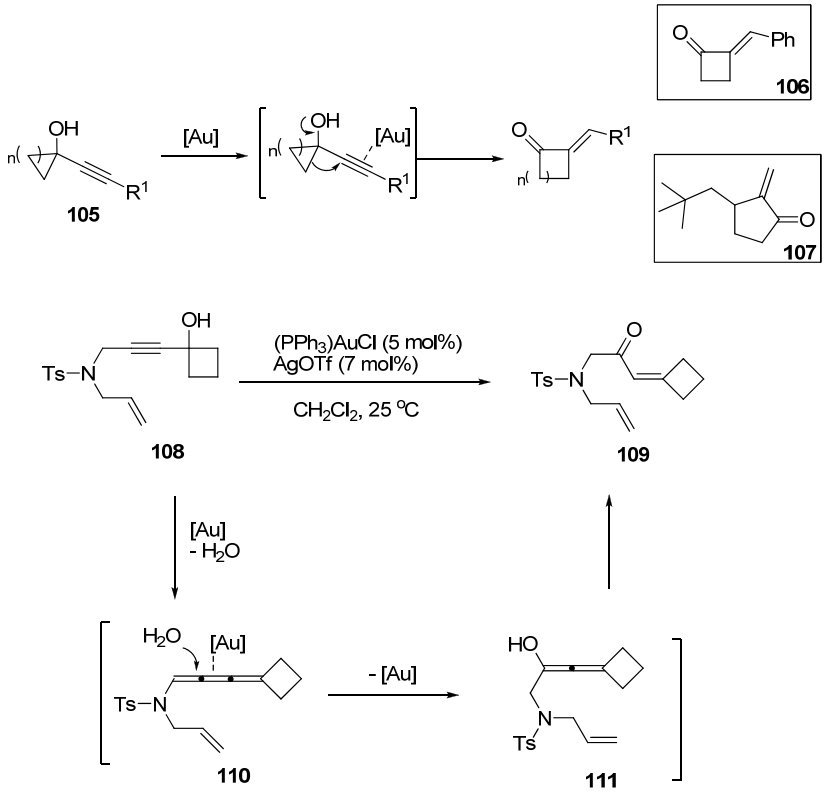
1.4. Synthetic applications of gold-catalyzed ring expansions

New methodologies catalyzed by late transition metals involving cycloisomerizations of strained rings such as cyclopropanes and cyclobutanes can open new venues for the synthesis of structurally more complex molecules.[68] The gold-catalyzed ring expansion of strained rings is already considered a mature synthetic tool in organic synthesis.[69]

1.4.1 Ring expansions involving oxygenated rings

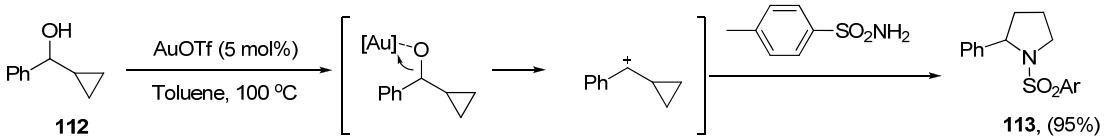
The gold-catalyzed ring expansion of cyclopropanols and cyclobutanols **105** is a versatile strategy for the synthesis of building blocks such as cyclobutanones and cyclopentanones (Scheme 38). Toste and coworkers[70] reported the synthesis of alkylidenecyclobutanone **106** and 2-metylene-3-neopentylcyclopentanone **107** through a process rationalized as a result of the π-activation of the triple bond in by the metal in alkynyl cyclopropanols followed by migration of the C-C bond and final 1,4-proton shift.[71] The outcome of the reaction changed dramatically using internal alkynyl cyclobutanols such as **108**, as reported by Chung and coworkers for the synthesis of α,β-unsaturated ketones **109**.[72] In the latter case the formation of cumulene **110** was proposed. Nucleophilic attack of a molecule of water onto the external gold-activated double bond of the cumulene gives the corresponding allenyl alcohol **111**, which tautomerized to deliver the α,β-unsaturated ketones **109**.

Scheme 38. Gold-catalyzed ring expansions of cyclopropanols and cyclobutanols



Pyrrolidines **113** can be efficiently synthesized from cyclopropylmethanols **112** in a tandem amination/ring expansion process (Scheme 39).[73] The reaction proceeds by the following sequence: activation of the cyclopropylmethanol **112** by the gold catalyst triggers the departure of the hydroxyl function followed by cyclopropyl ring opening. The new carbocation is trapped in the presence of the sulfonamide. Subsequent intramolecular hydroamination of the double bond affords the pyrrolidine product **113** in excellent yield.

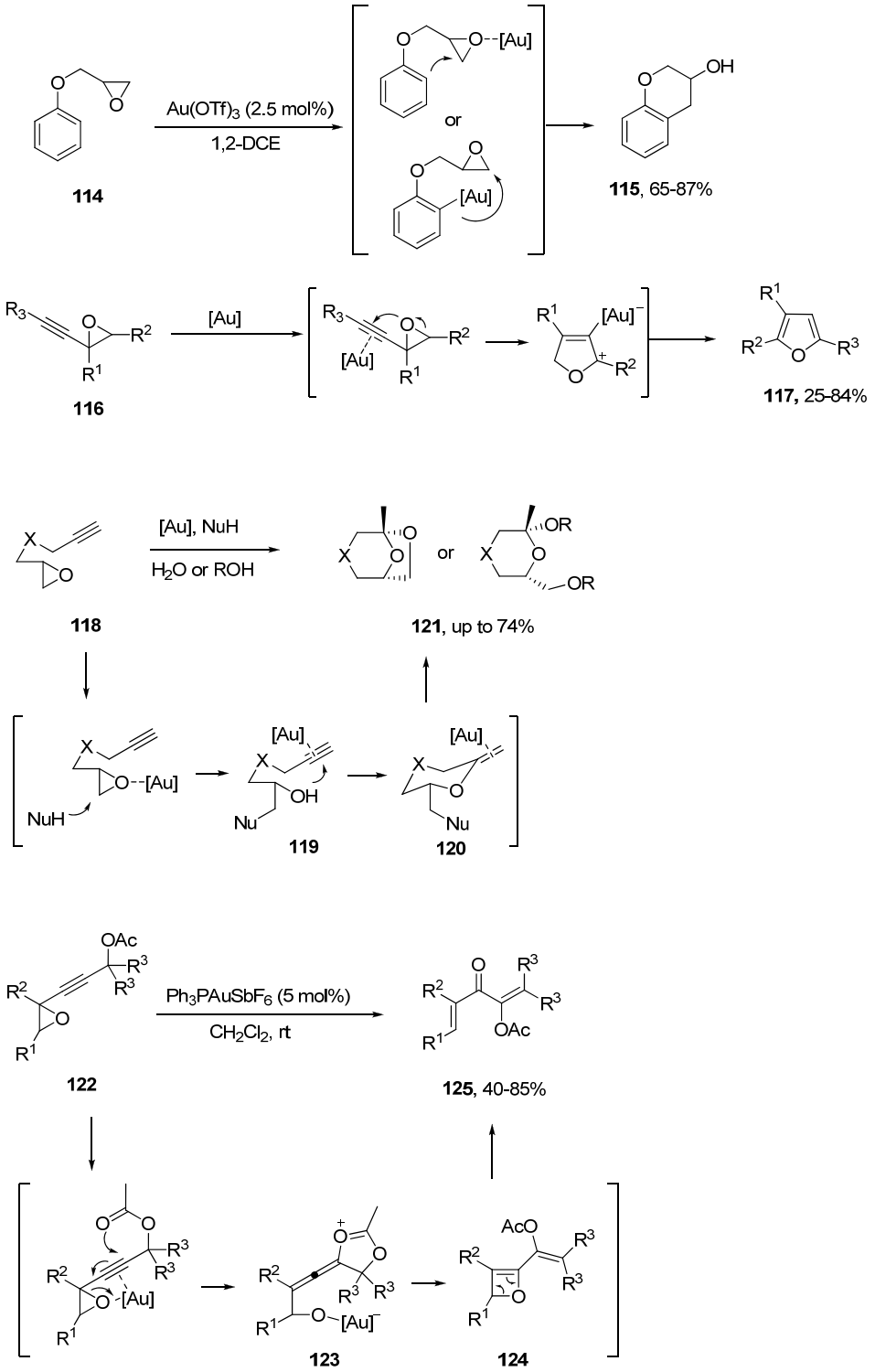
Scheme 39. Synthesis of pyrrolidine **113**



112 **113**, (95%)

Oxiranes can be efficiently activated by an oxophilic Lewis acid such as gold (Scheme 40). A good example is the gold-catalyzed ring opening of the aryl alkyl epoxide **114** for the synthesis of 3-chromanol **115**.[74] The authors proposed two types of mechanism that can explain the formation of the products through an aromatic auration step followed by the nucleophilic attack of the arylgold(III) onto the epoxides or a concerted mechanism where gold(III) purely activates the epoxide group triggering an electrophilic aromatic substitution reaction. Alkynyl epoxides **116** can be transformed into furans **117** *via* intramolecular nucleophilic addition of the oxirane oxygen atom onto the π-metal-alkyne complex.[75] The reaction seems to proceed through metal activation of the triple bond followed by cyclization. In a related method, the group of Shi has used epoxy alkynes **118**, which can be selectively transformed into ketals **121**. The reaction seems to commence with the epoxide ring opening in the presence of the nucleophile to give intermediate **119** followed by metal activation of the alkyne and intramolecular attack of the alcohol to give **120**. Reactivation of the olefin by the gold catalyst and subsequent incorporation of a second molecule of nucleophile (water or alcohol) affords ketals **121** in good yields. Acyloxylated alkynyl oxiranes **122** can be selectively transformed into divinyl ketones **125**. The authors proposed a reaction sequence that involves the coordination of the gold catalyst on both the alkynyl and oxirane moieties, rearrangement of the ester to deliver the allenic alcoholate **123**, which cyclizes to form the oxetane intermediate **124**. Cycloreversion in oxetane **124** furnishes the acyloxydivynyl ketones **125** in good yields.

Scheme 40. Gold-catalyzed cycloisomerization of oxiranes

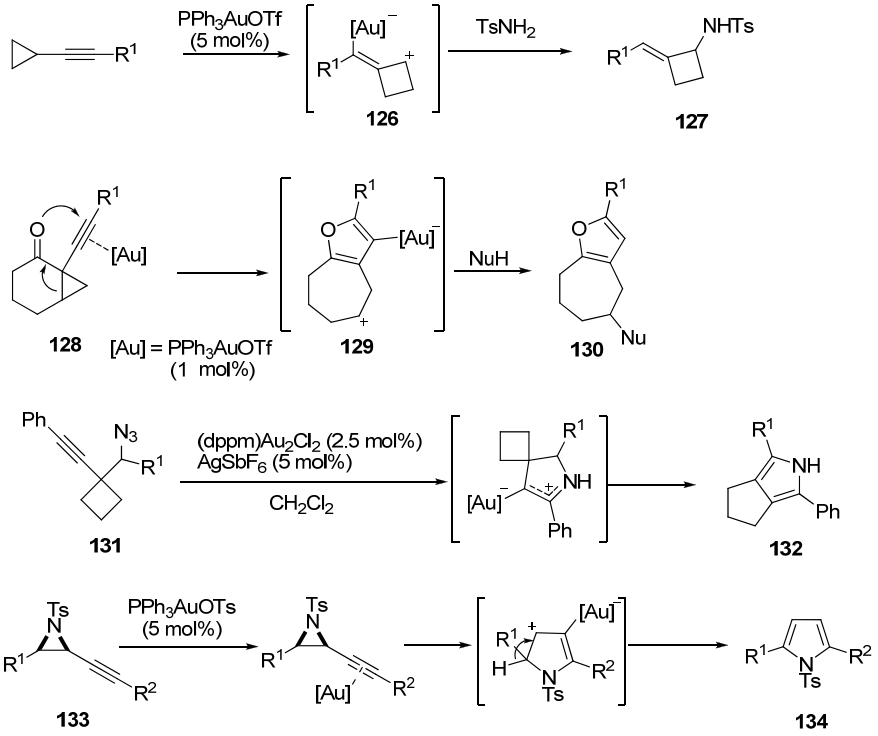


1.4.2 Ring expansions involving saturated alkyl rings

Metal-catalyzed ring expansions of cyclopropyl alkynes are a versatile method to access a wide range of building blocks.[76] Upon gold activation of the triple bond, a wide palette of transformations can be addressed either in an inter- or intramolecular fashion (Scheme 41). The

group of Yu[77] developed a synthesis of cyclobutanamines **127** in a process that involves a cyclopropyl ring expansion to form the cyclobutyl cation **126** followed by trapping of **126** with an external tosylamino nucleophile. Schmalz and coworkers[78] reported a gold-catalyzed cascade reaction of alkynyl cyclopropyl ketones **128** for the synthesis of cycloheptenylfurans **130**. In this process, the cyclopropyl ring triggers the nucleophilic attack of the carbonyl moiety onto the gold-activated alkyne to give the carbocationic intermediate **129**, which is trapped in the presence of external nucleophiles to afford furans **130**. Toste[79] and Davies[80] reported alternative routes for the synthesis of substituted pyrrols **132** and **134** using azides **131** and aziridines **133** moieties as starting materials respectively.

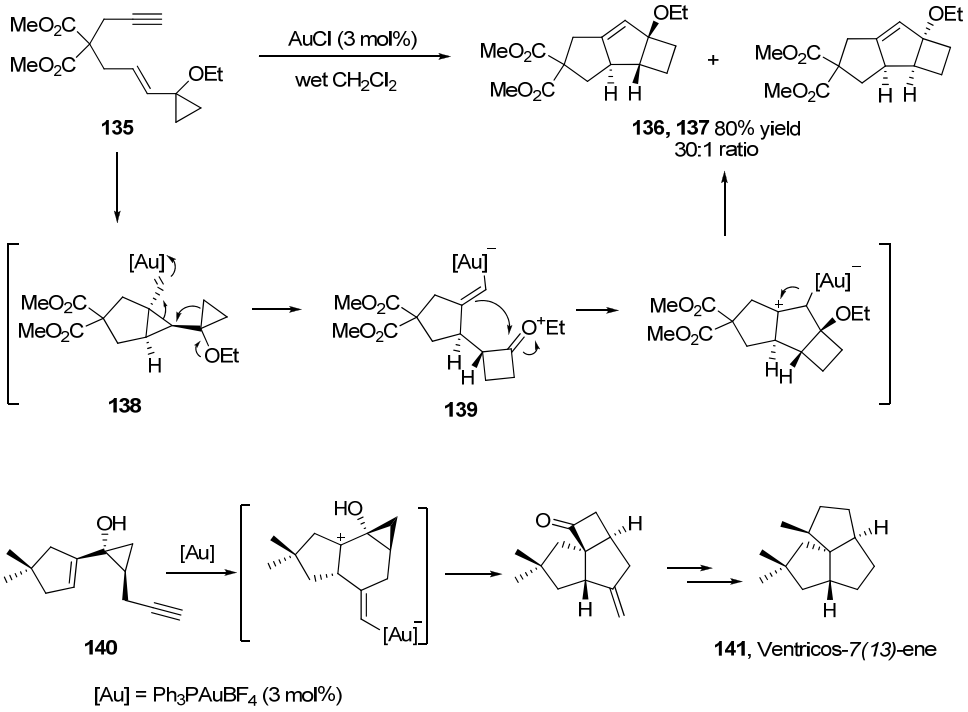
Scheme 41. Gold-catalyzed cycloisomerization of cyclopropyl alkynes



1.4.3 Ring expansions involving enynes

The combination of 1,6-enyne substrates and gold-catalyzed heteroatom-assisted 1,2-H-shift offers a synthetic tool towards the construction of molecular complexity (Scheme 42). Echavarren and coworkers[81] have successfully combined this reaction mode in a cycloisomerization process that involves a gold-catalyzed Prins cyclization of enynes **135** to afford *trans*- and *cis*-octahydrocyclobuta[*a*]pentalene skeletons **136** and **137**. The reaction seems to proceed in a concerted fashion *via* cyclopropyl carbene **138**, which undergoes ring expansion to afford the alkenyl-gold intermediate **139**. Nucleophilic attack of the vinyl-gold moiety onto the oxonium cation gives the tricyclic pentalene skeletons **136** and **137**. A remarkable synthetic application of this methodology has been reported by Toste and coworkers[82] applying the gold-catalyzed ring expansion of cyclopropanols with enynic substrates **140** for the synthesis of the angular triquinane ventricosene **141**.

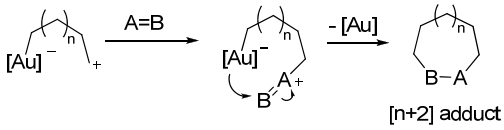
Scheme 42. Gold-catalyzed cycloisomerization of enynes **135** and cyclopropanols **140**



1.4.4 Ring expansions involving annulations reactions

The combination of gold-catalyzed ring expansions and annulation reactions is a powerful tool employed by organic chemists to construct molecular complexity. Dipoles have been usually described as transient, difficult to harness species towards cycloaddition reactions and can undergo many side reactions. Zhang envisioned that dipoles can be stabilized in its negative terminus by the presence of a gold catalyst triggering [*n*+*m*] annulations processes (Scheme 43). The cationic end of the dipole reacts with a dipolarophile in a bimolecular process to generate cycloadducts.[83]

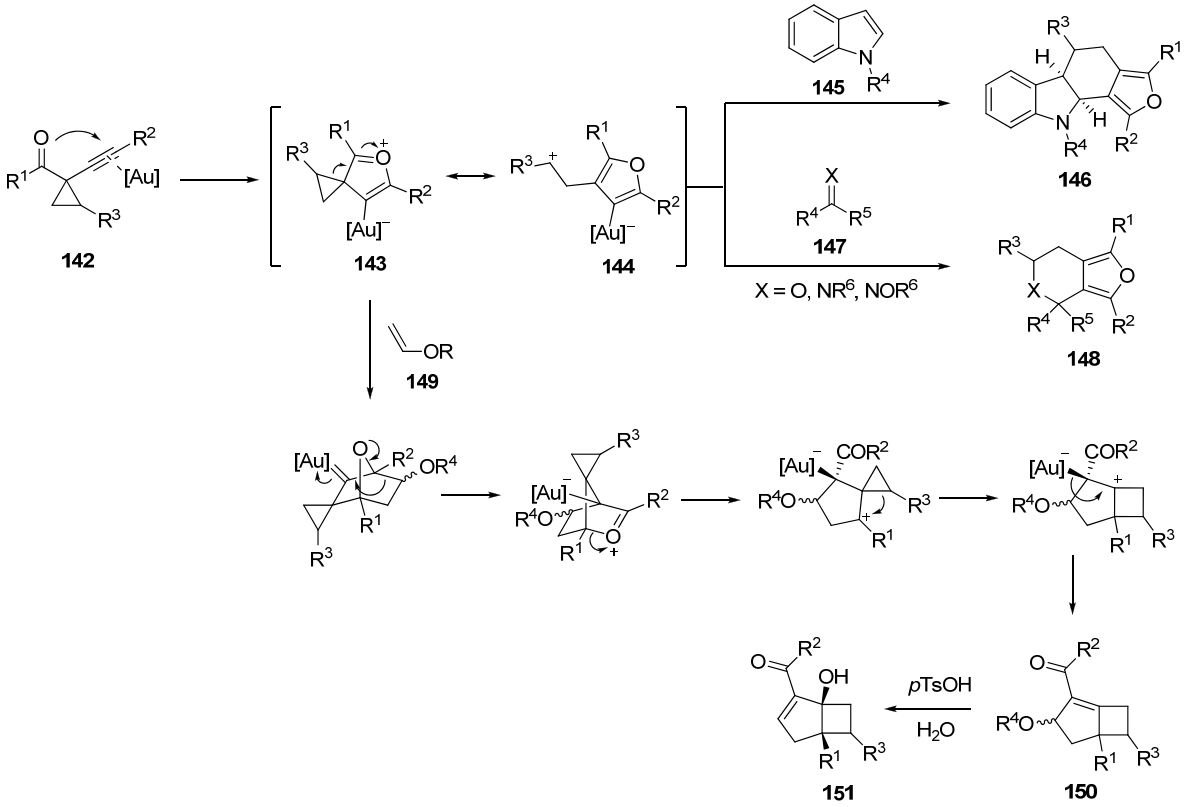
Scheme 43. Gold-catalyzed annulations processes



In this context, the gold-catalyzed ring expansion in cyclopropyl ketones can be used to generate 1,4-dipoles (Scheme 44). 1-(1-Alkynyl)cyclopropyl ketones **142**, in the presence of indoles **145**, afforded tetracyclic furans **146** in excellent yields. The mechanism for this transformation involves a [4+2] annulation reaction of the furan intermediate **144** that could be formed *via* oxocarbenium **143**. Furthermore, compounds **147** also reacted as dipolarophiles with the 1,4-furan dipole **144** in the presence of catalytic amounts of $AuCl_3$ for the synthesis of furans **148**.[84] In contrast, when alkoxy vinyl ethers **149** are employed,[85] the cyclization takes place prior to the formation of the furan intermediate **144**. In this case the bicyclic[3.2.0]heptane skeleton **151** is obtained in excellent yields upon 1,3-dipolar cycloaddition of the alkoxy vinyl ether **149** and the 1,4-dipole **143** followed by 1,2-alkyl migration and cyclopropyl ring expansion. The reaction

of **150** with a protic acid in water activates the enone system triggering the nucleophilic attack of water to give **151**.

Scheme 44. Gold-catalyzed synthesis of furans **146** and **148**.



1.5 Conclusions and Objectives

One of the most successful area in homogeneous catalysis falls into the ability of gold to coordinate unsaturated moieties. This mode of coordination can be explained as a donor-acceptor interaction between the metal and the ligand. According to the Dewar-Chatt-Duncanson model, a net shift of electron density is withdrawn from the unsaturated moiety to the metal doing the unsaturated C-C bond more electrophilic and thereby can be defined as π acid.

π-Bonds activated by gold can undergo a huge palette of transformations. The utility of gold complexes for the activation of alkynes towards the rearrangement of propargyl carboxylates has grown exponentially during the last years. Upon 1,2- or 1,3-acyl migration of the ester moiety onto the gold-activated alkyne, the formation of a vinyl-gold carbene or gold-activated allene open new venues for the construction of molecular complexity. The gold-catalyzed ring expansion of strained rings is considered as a powerful synthetic tool in organic chemistry.

The main objective of this thesis is the development of new methodologies involving a gold-catalyzed ring expansion of stabilized cyclopropyl rings for the synthesis of small complex molecules.

The chapter 2 and 3 of this PhD thesis will describe experimental studies into cyclopropyl ring opening expansions driven by gold-activation of alkynes and allenes for the synthesis of cyclopent-1-enyl acetates, cyclohexenones and cyclopentenyl ketones. In addition,

enantiomerically enriched cyclohexenones and cyclopentenyl ketones can be prepared by the gold-catalyzed cyclization of optically active propargyl acetates. Although the rearrangements are cationic in nature, the high degree of stereochemical information transfer in these reactions suggests that gold-stabilized nonclassical carbocations with a certain configurational stability are involved.

In the second part of this thesis (Chapter 4), a highly diastereoselective gold-catalyzed three-step cascade reaction for the synthesis of highly substituted five- and seven-membered rings from propargyl acetates and alkenes or 1,4-dienes will be described. The Cope rearrangement of propargyl acetates and 1,4-dienes represents an attractive alternative to previously reported Rh-catalyzed methodology for the synthesis of *cis*-2,3-disubstituted cyclopentenylacetates. In addition, the concerted nature of the process has allowed an alternative formal enantioselective total synthesis of both Frondosins A and B.

The last chapter of this PhD thesis (Chapter 5) will describe the role of both gold catalysts and acid for the activation of 1-cyclopropyl alkynes toward heteroaromatic nucleophiles. An efficient method to synthesize highly substituted tetrahydrocarbazoles *via* formation of a 1,5-dipole will be reported therein.

1.6 References

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Chapter 2

Gold-Catalyzed Cycloisomerization of 1-Cyclopropyl Alkynyl Acetates: A Versatile Approach to 5-, 6- and 7-Membered Carbocycles

CHAPTER 2

Gold-Catalyzed Cycloisomerization of 1-Cyclopropyl Alkynyl Acetates: A Versatile Approach to 5-, 6- and 7-Membered Carbocycles

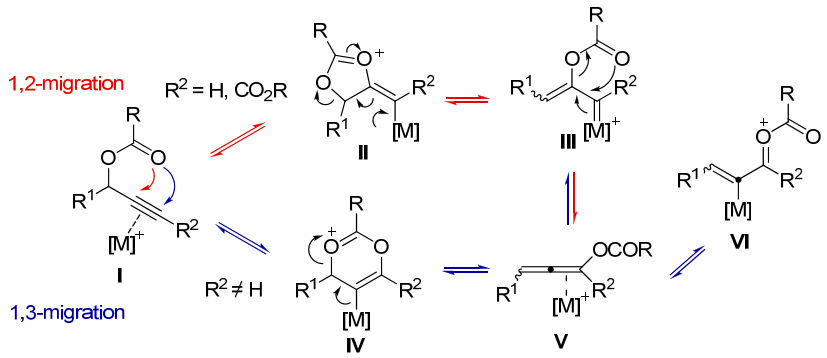
Y. Zou; D. Garayalde; Q. Wang*; C. Nevado* and A. Goeke*

(*Angew. Chem. Int. Ed.* **2008**, *47*, 10110-10113)

2.1 Introduction

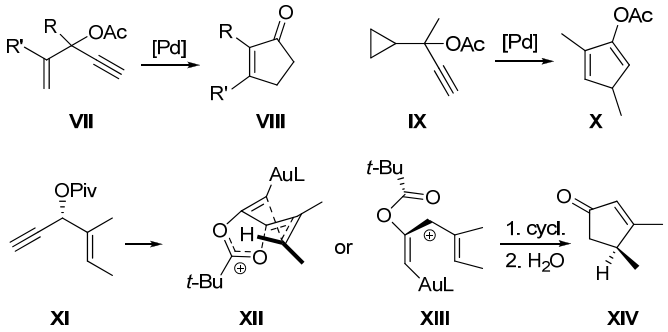
During the last decade, late transition metal catalyzed cycloisomerizations have emerged as a powerful tool to access unprecedented structural and mechanistical diversity.[1] In this context, a rapidly developing area involves the use of propargylic esters, preferably acetates, where the carbonyl unit acts as a nucleophile onto the metal-activated alkyne complex **I** (Scheme 1). Two distinctive mechanistic scenarios arise from this intermediate.[2] If terminal alkynes are used, 1,2 migration of the acetate affords vinyl metal species **II** which can result in the formation of a "carbenoid" **III**.[3] In contrast, internal alkynes undergo [3,3]-sigmatropic rearrangement forming allenyl acetates **V** which can be further activated in the presence of the metal catalyst to give **VI**, triggering also an extensive palette of transformations.[4,5]

Scheme 1. 1,2- *vs.* 1,3-acetate migration



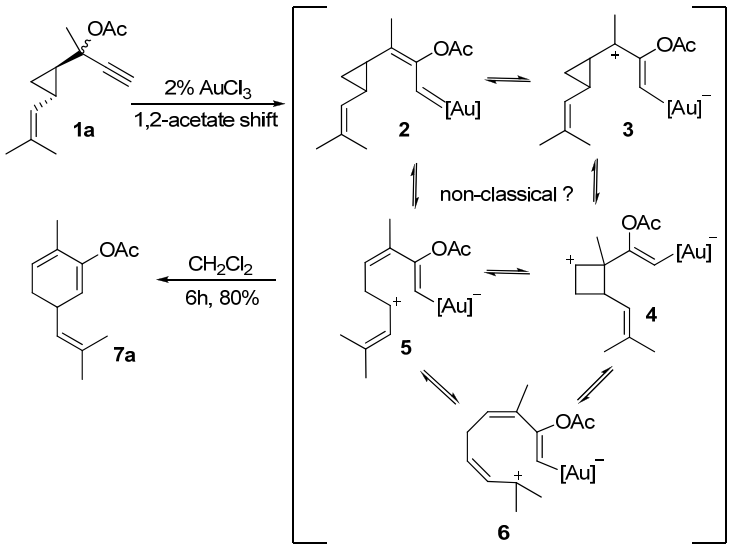
Intermediates of type **III** were proposed by Rautenstrauch in the Pd-catalyzed cycloisomerization/in situ hydrolysis of vinyl-propargyl acetates **VII** to 2-cyclopentenones **VIII** (Scheme 2).[6] One example of a conversion of cyclopropyl derivative **IX** to cyclopentadienyl acetate **X** was also reported. Recently, Toste et al. widely expanded the scope of this cyclopentenone synthesis by application of cationic Au(I) catalysts.[7] An interesting chirality transfer from an optically active propargyl pivaloate **XI** to the cyclopentenone **XIV** was postulated to proceed *via* cyclic oxonium ion **XII**, similar to mechanisms proposed for such conservation of stereochemical information in other cases.[8,9] In a subsequent calculation, the helical intermediate **XIII** was found to retain the stereochemical information of the starting material.[10]

Scheme 2. Pd- and Au-catalyzed cyclopentannulation



In order to access Rautenstrauch rearrangement products of larger ring sizes we decided to construct a homologous system **1a** (Scheme 3). The reaction in the presence of catalytic amounts of $AuCl_3$ aimed to probe the behavior of the canonical carbenoid **2** which could subsequentially arise from the Au-promoted 1,2-acetate migration.[3] However, to look at intermediate **2** with regard to the recently discussed nonclassical carbocationic nature of carbenoid-like intermediates of gold-catalyzed enyne cyclizations[1b,1g] could be more illuminative, as resonance structures **3**-**6** visualize the possibilities to undergo consecutive cyclizations more clearly: while intermediate **2** could lead to 7-membered ring products by Cope (divinylcyclopropane) rearrangement, the allylcations **5** and/or **6** may cyclize to 6- or 8-membered ring systems, respectively. We were pleased to find that compound **1a** exclusively led to cyclohexadienyl acetate **7a**. Herein, we report our investigation on this novel gold-catalyzed homo-Rautenstrauch rearrangement and hope it will help to further unravel the mechanistic blur of gold catalysis.

Scheme 3. Au-catalyzed homo-Rautenstrauch rearrangement

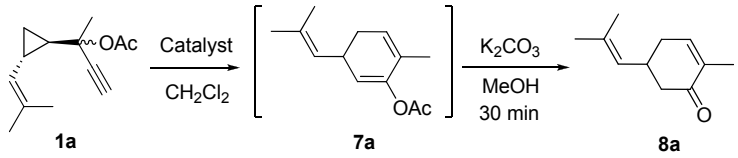


2.2 Results and discussion

To further broaden the insight into this initial result several optimization reactions were carried out. The primary product **7a** is a sensitive dienol acetate and it was generally converted to 2-hexenone **8a** by an in situ methanolysis during 30 min. In light of the previous success of

cationic gold(I) complexes for alkyne activation, compound **1a** was treated with a variety of such catalysts (Table 1). Using 1 mol% pregenerated cationic complex $Ph_3PAuSbF_6$ in CH_2Cl_2 produced acetate **7a** within 2 min and 85% isolated yield after hydrolysis (entry 2). Even at 0.1 mol% of catalyst loading, the reaction was fast and no significant decrease in yield was observed (entry 3). Interestingly, decomposition of substrate **1a** was observed when changing the counterion from SbF_6^- to TfO^- (entry 4). Control experiments employing either 5 mol% Ph_3PAuCl or 5 mol% $AgSbF_6$ as the sole catalyst did not lead to any product **7a** (Table 1, entries 5 and 6). Notably, under the original reaction condition reported by Rautenstrauch,[6] decomposition of **1a** was observed (entry 7).

Table 1. Catalyst optimization.

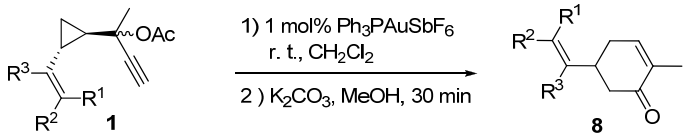


Entry	Catalyst (mol%)	t (min)	Yield (%)[a]
1	$AuCl_3$ (2%)	360	75
2	$Ph_3PAuSbF_6$ (1%)	2	85
3	$Ph_3PAuSbF_6$ (0.1%)	30	80
4	$Ph_3PAuOTf$(5%)	5	0[b]
5	Ph_3PAuCl (5%)	360	0[c]
6	$AgSbF_6$ (5%)	5	0[b]
7	$PdCl_2(MeCN)_2$	360	0[b]

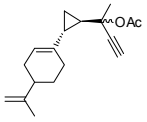
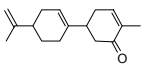
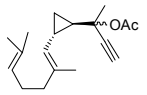
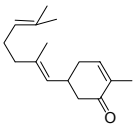
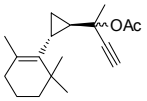
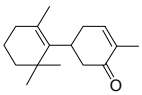
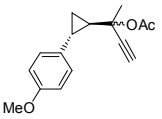
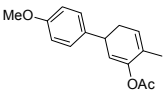
[a] Yield of isolated product **8a** after column chromatography. [b] Decomposition occurred. [c] Starting material was recovered.

With good working conditions in hand, the scope of the gold(I)-catalyzed cycloisomerization of 1-cyclopropyl-propargyl esters **1** was examined (Table 2). The reactions were all carried out on gram scale under very mild conditions. In none of the cases cyclopentenones were detected. Alkyl (Table 2, entries 1-4) and aryl (entry 5) substitutions at the double bonds were tolerated and products **8** were obtained in good to excellent yields. As expected, sterically hindered substrate **1i** resulted in a slower reaction, but full conversion was achieved after 6 h, giving bicyclic compound **8i** in an excellent isolated yield of 90% (entry 8). The cyclopropyl ring cleavage can be also stabilized by a *para*-methoxyphenyl substituent (**1j**) affording **7j** in good yield (entry 9).

Table 2. Scope of the Au(I)-catalyzed 2-cyclohexenone synthesis.[a]



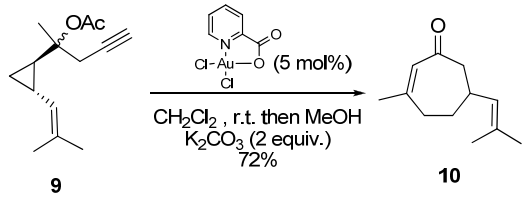
Entry	Substrate	Product	t (min)[b]	Yield (%)[c]
1	**1b** R^1=R^2=Et, R^3=H	**8b**	5	78
2	**1c** R^1=H, R^2=*n*-Pr, R^3=H	**8c**	10	62
3	**1d** R^1=CH_3, R^2=Et, R^3=H	**8d**	10	82
4	**1e** R^1=H, R^2=Et, R^3=CH_3	**8e**	10	96

5	**1f** R^1=H, R^2=Ph, R^3=CH_3	**8f**	10	88[11]
6	 **1g**	 **8g**	10	56
7	 **1h**	 **8h**	10	71
8	 **1i**	 **8i**	360	90
9	 **1j**	 **7j**	60	70[d]

[a] Conditions: (1) Substrate (10 mmol, 1 M in CH_2Cl_2), $Ph_3PAuSbF_6$ (1mol% in CH_2Cl_2), RT. (2) K_2CO_3 (20 mmol), MeOH (10 mL), RT, 30 min. [b] Reaction time for the first step with 100% conversion determined by GC-MS. [c] Isolated yield after 2 steps. [d] Isolated yield after the first step.

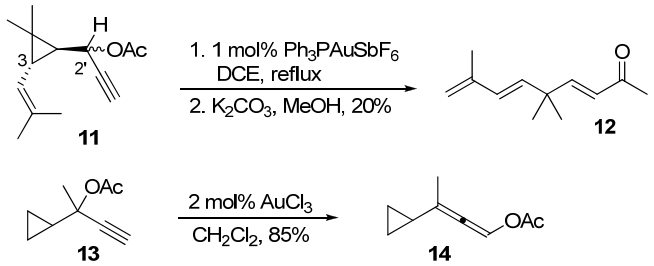
We could also extent this process to homopropargyl acetates, which have been reported to undergo acetate migration to the internal alkyne position, although serious limitations were observed when restricted conformations were not achieved.[12] To our delight, cyclization of substrate **9** occured smoothly affording cycloheptenone **10** in 72% yield (Schme 4).

Scheme 4. Homopropargyl acetate cycloisomerization



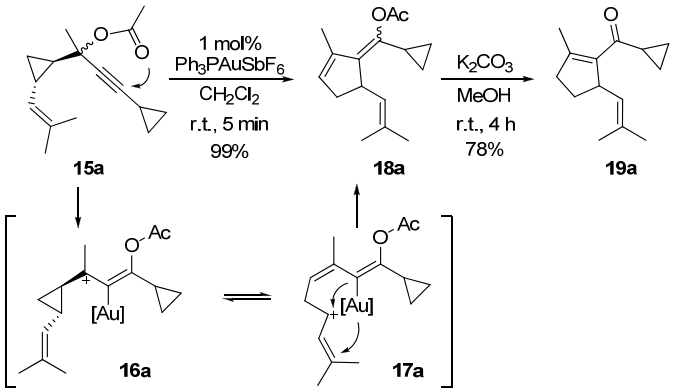
Apparently, the stabilization of positive charge in intermediates **3** and **5** (Scheme 3) is essential for a smooth conversion of **1** to cyclization products **7**: even under harsh conditions, secondary acetate **11** did not cyclize but ring-opened to trienone **12** after hydrolysis, albeit in low yield (Scheme 5). Likewise, the simple cyclopropyl derivative **13** did not cyclize but rearranged to allene **14**.

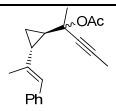
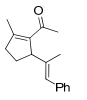
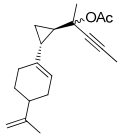
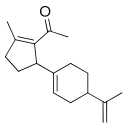
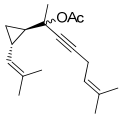
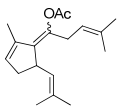
Scheme 5. Side reactions of the cycloisomerization



As shown in Scheme 1, substitution at the terminal position of the acetylene unit may initiate a 6-*endo*-*dig*-like 1,3-migration of the carboxylate group.[2,4] We envisioned that substrates such as **15a** would generate, by treatment with $Ph_3PAuSbF_6$, cyclopropylalkyl carbenium ion **16a** which is mesomeric to intermediate **17a** (Table 3). Cyclization of these species at the allyl cationic positions may occur, but only trienyl acetate **18a** was obtained in almost quantitative yield as a mixture of *cis/trans* isomers. Methanolysis with concomitant isomerization led to **19a** as a single isomer. Further investigation (Table 3) revealed that the cyclization also tolerates a variety of differently substituted substrates.

Table 3. Scope of the Au (I) catalyzed 1-cyclopentenylketone synthesis.[a]



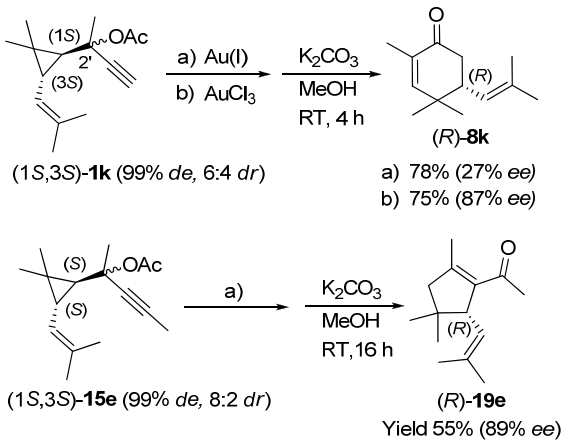
Entry	Substrate	Product	t (min)[b]	Yield (%)[c]
1	 **15b**	 **19b**	5	88
2	 **15c**	 **19c**	2	87
3	 **15d**	 **18d**	10	90[d]

[a] Conditions: (1) Substrate (10 mmol, 1 M in CH_2Cl_2), $Ph_3PAuSbF_6$ (1mol% in CH_2Cl_2), RT. (2) K_2CO_3 (20 mmol), MeOH (10 mL), RT, 16 h. [b] Reaction time of first step with 100% conversion determined by GC-MS. [c] Isolated yield after column chromatography. [d] Yield of isolated product **18d** after column chromatography.

The interesting question of a possible chirality transfer in these systems was addressed using optically active substrates **1k** and **15e**, both easily available from optically pure (1*S*,3*S*)-(−)-*trans*-chrysanthemum acid (99% ee) (Scheme 6).[13] Cycloisomerization of **1k** (dr = 6:4, 99% de) under standard conditions ($Ph_3PAuSbF_6$, CH_2Cl_2, rt) cleanly afforded (*R*)-**8k** after methanolysis, however, with only 27% ee. Lowering the temperature to -20 °C only increased the reaction time to 24 h without significantly improving the ee value (31% ee). Performing the reaction in various solvents did not improve these results either. Surprisingly, using $AuCl_3$ as catalyst retained the

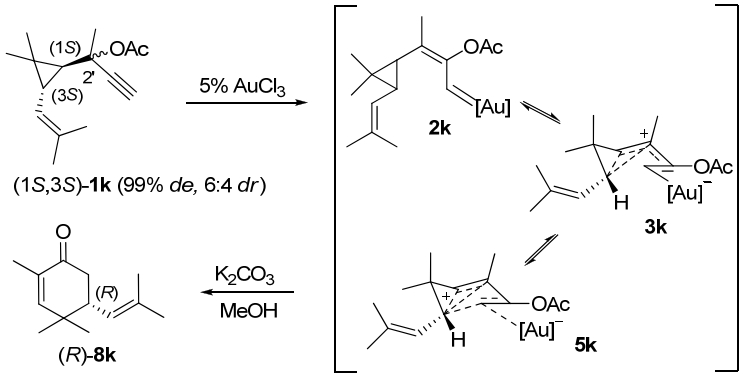
enantioselectivity most effectively, leading to (*R*)-**8k** with 87% ee. On the other hand, $Ph_3PAuSbF_6$-promoted cycloisomerization of compound **15e** delivered acetylcyclopentenone (*R*)-**19e** with good chirality transfer (89% ee) (Scheme 6). The absolute configurations of (*R*)-**8k** and (*R*)-**19e** were determined by comparing the vibrations of a measured ROA (Raman Optical Activity) spectra with those of the theoretical spectra, calculated at the B97-1/pc-2 level with the Gaussian program. ROA calculations at the TDHF/DPS level were carried out with the Dalton program.[14]

Scheme 6. Chirality transfer of compounds **1k** and **15e** to 6- and 5-membered ring products



In our view, these results disfavor intermediates analogous to **XII** or **XIII** (Scheme 2) since the stereochemical information of the position 2' in substrate **1k** (Scheme 6) does not overrule that inherent at C1 and C3.[15] In contrast, as the reaction depends on stabilization of positive charge in particular at positions 3 and 2' in **1k** (see Scheme 4 and ref. 12), but only to an extent that prevents formation of the achiral cation **5** (Scheme 3), we propose a more concerted mechanism, where carbene **2k** can be also redefined as nonclassical carbonium ion[1,16]complex **3k** or, under participation of the vinyl-gold unit species **5k**,[17] as the enantioselectivity preserving intermediate (Scheme 7). Depending on the electronic stabilization and geometry, these species display a certain configurational stability by which stereochemical information is retained throughout the reaction.

Scheme 7. Proposed non-classical intermediates for the chirality transfer to product **8k**.



2.3 Conclusion

In conclusion, we have found a new Au-catalyzed homo-Rautenstrauch rearrangement of 1-cyclopropylpropargylic esters to cyclohexenones **8** and cyclopentenyl ketones **19** under mild conditions. In addition, enantiomerically enriched cyclohexenones and cyclopentenyl ketones can be prepared by the gold-catalyzed cyclization of optically active propargyl acetates. Although the rearrangements are cationic in nature, the high degree of chirality transfer in these reactions suggests that gold-stabilized nonclassical carbocations with a certain configurational stability are involved. Further studies to elucidate the homologization strategy by gold-promoted cycloisomerizations of cyclopropane derivatives to novel products are underway.

2.4 References

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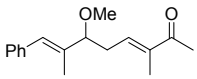
[11] When the reaction was performed using $AuCl_3$ and MeOH as solvent, substrate **1f** reacted via 1,2-acetate shift and solvolysis of the cyclopropane unit to a methoxy adduct:



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[15] A diastereomeric ratio of 6:4 would account for a chirality transfer of a maximum 20% ee.

[16] a) For a general review on nonclassical cations, see: Olah, G.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev*. **1992**, *92*, 69-95. b) For a related case, see: Motamed, M.; Brunnelle, E. M.; Singaram, S. W.; Sharpong, R. *Org. Lett*. **2007**, *9*, 2167-2170.

[17] Species **3k** (see also **3** in Scheme 3) could be most likely represented as the *E* configured vinyl gold intermediates. Nevertheless, *Z* isomer has been postulated to be plausible, being generated by anchimeric assistance allowing the cyclization with minimal steric hindrance (ref. 9a).

Chapter 2

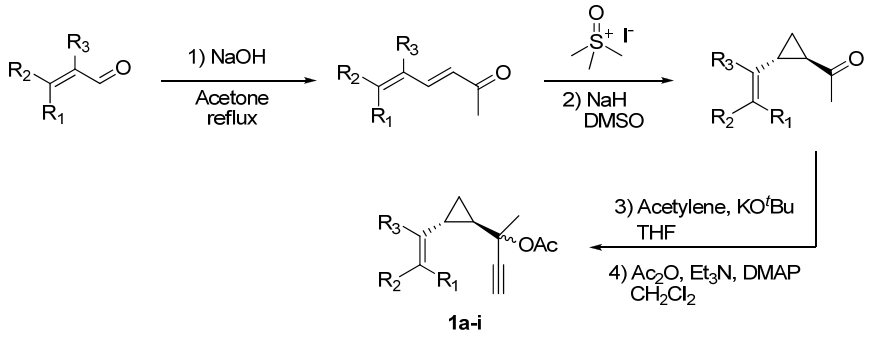
Experimental Section

Contents:

1. General information

^{1}H and ^{13}C NMR spectra were recorded with AW 300 and AV2 400 MHz Bruker spectrometer instruments in $CDCl_3$. Chemical shifts in $CDCl_3$ and CD_2Cl_2 are reported in δ (ppm) relative to tetramethylsilane (TMS), chloroform and dichloromethane as internal reference unless otherwise stated. In the ^{13}CNMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT 90 and DEPT-135 experiments, and is given in parentheses. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, bs = broad singlet, sept = septet. Solvents for extraction and chromatography were technical grade and used without further purification. Flash chromatography was performed using Tsingdao Haiyang Chemical silica gel (200 ± 300 mesh) and silica gel Merck grade (60 Å). Unless otherwise noted, a mixture of hexane:MTBE (50:1) was used as eluent. IR spectra were recorded with a Bruker Tensor 27 and a Jasco FT/IR-4100. High resolution MS were obtained with a Finnigan MAT 95 (San Jose, CA; USA) double-focusing magnetic sector mass spectrometer (geometry BE) and GC/MS spectral data were obtained from an Agilent 6890 N and MSD 5975 using a column HP-5 MS, 30 m, 0.25 mm, 0.25 μm. The enantiomeric excess (ee) of **8k** and **19e** were determined by GC in comparison to the corresponding racemic samples using MN HYDRODEX-beta-6TBDM column (25 m x 0.25 mm, program 80-150 °C, 2 °C /min, Helium carrier pressure 13.2 psi, FID detection (250°C) .

2. General experimental procedure for the preparation of 2-(2-vinylcyclopropyl)but-3-yn-2-yl acetates (compounds 1a-j):



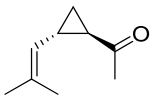
1) Sodium hydroxide (0.4g, 0.01 mol) was added to a solution of an *α,β*-unsaturated aldehydes **20** (0.5 mol) in acetone (200 mL). The reaction mixture was refluxed for 2 hours and then cooled to room temperature. After neutralization with 1 N HCl solution, the mixture was concentrated and partitioned with MTBE and water. The organic layer was washed with brine (200 mL), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by distillation to give crude hexa-3,5-dien-2-ones which were pure enough for further transformations (yield 30-60%).

2) To a suspension of trimethyl sulfoxonium iodide (20 mmol) in DMSO (30 mL) with vigorous stirring was added sodium hydride (20 mmol, 60% in mineral oil) in 3 portions under argon atmosphere. After 30 min, the reaction mixture was cooled to 0 ^oC and crude hexa-3,5-dien-2-one (20 mmol) prepared above was added dropwise. The mixture was stirred at RT for 16 h, cooled to 0 ^oC, quenched with water (150 mL) and extracted 3 times with MTBE (100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent:hexane/MTBE = 50/1) to give the corresponding 1-(2-vinyl-cyclopropyl)-ethanone **22**.

3) Acetylene gas was bubbled through a solution of KO*t*Bu (20 mmol) in THF (100 mL) until saturation was reached. Then, ketone **22** (10 mmol) was added dropwise to the viscous suspension. The mixture was stirred for 2 hours until completion of the reaction. Water (150 mL) was added and the mixture was extracted 3 times with MTBE (100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated in vacuo to give the crude propargylic alcohol of larger than 95% purity (GC). This material was directly used in the next step.

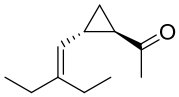
4) Acetic anhydride (4.8 mL, 50 mmol) was added to a solution of the propargylic alcohol (10 mmol), Et_3N (14 mL, 100 mmol) and DMAP (0.12g, 1.0 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C. The reaction was stirred at room temperature for 24 h, was concentrated and partitioned between MTBE and water. The organic layer was washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled bulb to bulb to give the desired acetate **1a-i**.

***rac-trans*-1-(-2-(2-Methylprop-1-enyl)cyclopropyl)ethanone (22a)**



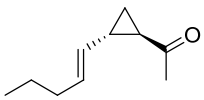
22a Yield 80%, colorless liquid. The analytical results are in accordance to the reference data.[1]

***rac-trans*-1-(-2-(2-Ethylbut-1-enyl)cyclopropyl)ethanone (22b)**



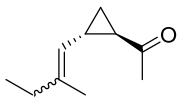
22b Yield 50%, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.55 (d, *J* = 9.2 Hz, 1H), 2.26 (s, 3H, $COCH_3$), 2.13 (q, *J* = 7.5 Hz, 2H, $CH_2(CH_3)$a), 2.12-2.06 (m, 1H), 2.03 (q, *J* = 7.5 Hz, 2H, $CH_2(CH_3)$b), 1.96-1.87 (m, 1H), 1.53-1.42 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H, $CH_2(CH_3)$a), 0.95 (t, *J* = 7.5 Hz, 3H, $CH_2(CH_3)$b), 0.96-0.91 (m, 1H) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 207.4 (s), 145.4 (s), 122.9 (d), 30.7 (d), 30.6 (q), 29.0 (t), 24.8 (d), 23.9 (t), 18.6 (t), 13.1 (q), 12.5 (q) ppm. GC/MS (EI): 166 (M+, 30), 151 (2), 137 (10), 123 (59), 108 (6), 95 (33), 81 (100), 67 (41), 55 (23), 43 (59). IR (neat, ν/cm-1): 2966, 2935, 1697, 1462, 1433, 1400, 1379, 1173, 967, 855. HRMS (EI): m/z: calcd. for $C_{11}H_{18}O$ 166.1358; found: 166.1346.

***rac-trans*-1-(2-((*E*)-Pent-1-enyl)cyclopropyl)ethanone (22c)**



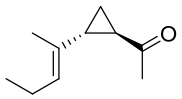
22c Yield 38%, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.65-5.52 (m, 1H), 5.02 (dd, *J* = 15.3, 8.3 Hz, 1H), 2.25 (s, 3H, $COCH_3$), 2.18-1.86 (m, 4H), 1.60-1.30 (m, 3H), 1.04-0.95 (m, 1H), 0.93 (t, *J* = 7.3 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.1 (s), 131.3 (d), 129.9 (d), 34.4 (t), 30.5 (q), 30.4 (d), 27.9 (d), 22.4 (t), 19.8 (t), 13.6 (q) ppm. GC/MS (EI): 152 (M+, 13), 137 (3), 123 (20), 109 (47), 95 (23), 79 (25), 67 (97), 55 (15), 43 (100). IR (neat, ν/cm-1): 3003, 2960, 2929, 1699, 1450, 1437, 1397, 1357, 1173, 962, 592. HRMS (EI): m/z: calcd. for $C_{10}H_{16}O$ 152.1201; found: 152.1197.

***rac*-1-(2-(2-Methylbut-1-enyl)cyclopropyl)ethanone (22d)**



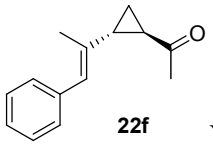
22d Yield 55%, colorless liquid. Mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.60 (d, *J* = 8.2 Hz, 1H), 2.26 (s, 3H, $COCH_3$), 2.18-2.04 (m, 2H), 1.98 (q, *J* = 7.4 Hz, 1H), 1.89 (m, 1H), 1.71, 1.67 (2s, 3H, CH_3), 1.50-1.45 (m, 1H), 1.06-0.94 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.94-0.86 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.3, 207.2 (s), 139.7, 139.3 (s), 124.5, 123.3 (d), 32.0, 31.5 (t), 30.6, 24.7 (d), 30.5, 30.4 (q), 25.3, 18.5 (t), 24.7, 24.6 (d), 16.5 (q), 12.6, 12.4 (q) ppm. GC/MS (EI): 152 (M+, 28), 137 (3), 123 (6), 109 (88), 95 (29), 81 (35), 67 (89), 55 (29), 43 (100). IR (neat, ν/cm-1): 2966, 2934, 1697, 1434, 1397, 1360, 1174, 963, 915. HRMS (EI): m/z: calcd. for $C_{10}H_{16}O$ 152.1201; found: 152.1197.

***rac-trans*-1-(2-((*E*)-Pent-2-en-2-yl)cyclopropyl)ethanone (22e)**[2]



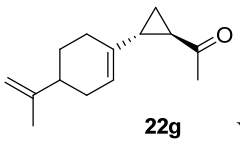
22e Yield 50%, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.25 (t, *J* = 7.1 Hz, 1H), 2.25 (s, 3H, $COCH_3$), 2.07-1.92 (m, 4H), 1.51 (s, 3H), 1.35-1.28 (m, 1H), 1.16-1.09 (m, 1H), 0.95 (t, *J* = 7.5 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.5 (s), 131.8 (s), 127.7 (d), 33.0 (d), 30.4 (q), 28.7 (d), 21.0 (t), 15.7 (t), 14.0 (q), 13.9 (q) ppm. GC/MS (EI): 152 (M+, 2), 137 (8), 123 (11), 109 (100), 93 (15), 81 (26), 67 (52), 55 (19), 43 (77). IR (neat, ν/cm-1): 2963, 2933, 1698, 1439, 1399, 1356, 1319, 1173, 965, 592.

***rac-trans*-1-(2-((*E*)-1-Phenylprop-1-en-2-yl)cyclopropyl)ethanone (22f)**



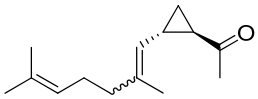
22f Yield 85%, yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.18 (m, 5H, Ar-H), 6.38 (s, 1H), 2.30 (s, 3H, $COCH_3$), 2.23-2.09 (m, 2H), 1.76 (s, 3H, CH_3), 1.50-1.40 (m, 1H), 1.31-1.25 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.2 (s), 137.7 (s), 136.0 (s), 128.8 (d), 128.1 (d), 126.3 (d), 125.9 (d), 33.7 (d), 30.6 (q), 28.9 (d), 16.1 (d), 15.6 (q) ppm. GC/MS (EI): 200 (M+, 9), 185 (5), 167 (4), 157 (100), 142 (45), 129 (57), 115 (31), 91 (19), 77 (8), 43 (17). IR (neat, ν/cm-1): 3022, 1697, 1492, 1397, 1355, 1179, 700. HRMS (EI): m/z: calcd. for $C_{14}H_{16}O$ 200.1201; found: 200.1207.

1-(2-(4-(Prop-1-en-2-yl)cyclohex-1-enyl)cyclopropyl)ethanone (22g)



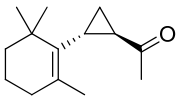
22g Yield 62%, yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.55-5.50 (m, 1H), 4.72 (s, 1H), 4.70 (s, 1H), 2.25 (s, 3H, $COCH_3$), 2.18-2.02 (m, 2H), 2.00-1.78 (m, 6H), 1.73 (s, 3H, CH_3), 1.52-1.37 (m, 1H), 1.36-1.22 (m, 1H), 1.20-1.06 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.5 (s), 149.6 (s), 135.0 (s), 121.9, 121.7 (d), 108.6 (t), 41.0 (d), 31.3 (d), 30.6 (t), 30.4 (q), 28.4 (d), 27.5 (t), 27.0 (t), 20.7 (q), 15.9, 15.3 (t) ppm. GC/MS (EI): 204 (M+, 6), 189 (5), 161 (75), 146 (19), 131 (18), 119 (37), 105 (45), 91 (87), 77 (47), 67 (23), 53 (19), 43 (100). IR (neat, ν/cm-1): 2920, 1698, 1437, 1399, 1355, 1177, 888. HRMS (EI): m/z: calcd. for $C_{14}H_{20}O$ 204.1514; found: 204.1511.

***rac*-1-(2-(2,6-Dimethylhepta-1,5-dienyl)cyclopropyl)ethanone (22h)**



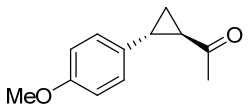
22h Yield 46%, yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.08 (t, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 9.1 Hz, 1H), 2.25 (s, 3H, $COCH_3$), 2.18-1.86 (m, 5H), 1.73 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.50-1.40 (m, 1H), 1.25-0.90 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.4, 207.2 (s), 137.8, 137.6 (s), 131.8, 131.6 (s), 125.6, 124.7 (d), 124.0, 123.9 (d), 39.4, 32.5 (t), 30.6 (d), 26.5, 26.4 (t), 25.6 (q), 25.0 (d), 23.2 (q), 18.5, 18.4 (t), 17.6 (q), 16.7 (q) ppm. GC/MS (EI): 206 (M+, 8), 191 (2), 163 (12), 148 (30), 137 (22), 121 (8), 107 (14), 95 (58), 79 (25), 69 (100), 53 (10), 43 (91). IR (neat, ν/cm-1): 2967, 2920, 1698, 1435, 1398, 1360, 1173, 1107, 967. HRMS (EI): m/z: calcd. for $C_{14}H_{22}O$ 206.1671; found: 206.1672.

***rac*-1-(2-(2,6,6-Trimethylcyclohex-1-enyl)cyclopropyl)ethanone (22i)**[3]



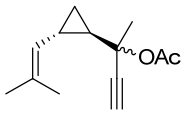
22i Yield 8%, colorless liquid. Data obtained match the reference data.[4] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, $COCH_3$), 2.20-1.84 (m, 4H), 1.66 (s, 3H, CH_3), 1.64-1.32 (m, 5H), 1.20-1.16 (m, 1H), 1.12 (s, 3H, CH_3), 1.02 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.4 (s), 134.6 (s), 131.8 (s), 41.1 (t), 35.2 (s), 33.4 (t), 30.5 (q), 30.3 (d), 39.1 (q), 29.0 (q), 26.5 (d), 20.8 (q), 19.1 (t), 19.0 (t) ppm. GC/MS (EI): 206 (M+, 20), 191 (29), 173 (6), 163 (27), 147 (25), 135 (37), 121 (40), 107 (86), 91 (63), 79 (37), 69 (45), 55 (29), 43 (100). IR (neat, ν/cm-1): 2930, 2867, 1698, 1458, 1359, 1254, 1173, 976.

***rac-trans*-1-(2-(*p*-Methoxyphenyl)cyclopropyl)ethanone (22j)**



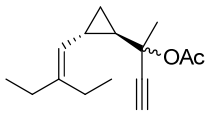
22j Yield 80%, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04-7.01 (m, 2H), 6.84-6.81 (m, 2H), 3.78 (s, 3H, OCH_3), 2.51-2.46 (m, 1H), 2.29 (s, 3H, $COCH_3$), 2.16-2.12 (m, 1H), 1.65-1.61 (m, 1H), 1.35-1.30 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 158.3, 132.2, 127.2, 113.9, 55.3, 32.7, 30.7, 28.5, 18.8 ppm. MS (EI): 190.1 (M+, 31), 148 (11), 147 (100), 132 (10), 131 (7), 117 (7), 116 (6), 115 (15), 103 (8), 91 (18), 43 (14). IR (neat, ν/cm-1): 1693, 1612, 1514, 1394, 1245, 1179, 1166, 1034, 828, 818 537. HRMS (EI): m/z: calcd. for $C_{12}H_{14}O_2$ 190.0980; found: 190.0992.

***rac*-2-(2-(2-Methylprop-1-enyl)cyclopropyl)but-3-yn-2-yl acetate (1a)**



1a Purified by distillation under reduced pressure to give a colourless liquid. Yield 80%. B.p. 110-113 °C/0.07 mbar. 2 Isomers in a ratio of 6:4. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.66-4.59 (m, 1H), 2.52, 2.51 (s, 1H), 2.04, 2.03 (s, 3H), 1.76, 1.75 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H), 1.32-1.10 (m, 2H), 0.98-0.89 (m, 1H), 0.62-0.49 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 169.2 (s), 132.0, 131.8 (s), 126.3, 126.1 (d), 81.2 (s), 76.8, 76.7 (s), 73.9, 73.8 (d), 28.5 (d), 27.2, 27.0 (q), 25.5, 25.4 (q), 21.9 (q), 18.2 (q), 15.9, 15.4 (d), 12.0, 10.9 (t) ppm. GC/MS (EI): 206 (M+, 1), 164 (7), 146 (28), 131 (100), 115 (36), 105 (33), 82 (94), 67 (34), 53 (20), 43 (77). IR (neat, ν/cm-1): 2980, 2927, 1747, 1446, 1369, 1241, 1074. HRMS (EI): m/z: calcd. for $C_{13}H_{18}O_2$ 206.1307; found: 206.1285.

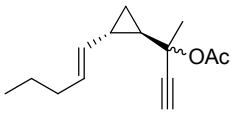
***rac*-2-(2-(2-Ethylbut-1-enyl)cyclopropyl)but-3-yn-2-yl acetate (1b)**



1b Purified by distillation under reduced pressure to give a colourless liquid. Yield 78%. B.p. 125-130 °C/0.04 mbar. 2 isomers in a ratio of 6:4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.55-4.53 (m, 1H), 2.51 (s, 1H), 2.25-1.62 (m, 4H), 2.03, 2.01 (s, 3H), 1.75 (s, 3H), 1.33-1.26 (m, 1H), 1.18-1.11 (m, 1H), 1.05-0.93 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H), 0.61-0.51 (m, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.3 (s), 143.4, 143.2 (s), 124.3, 124.2 (d), 81.3 (s), 76.9 (s), 73.9 (d), 28.9 (t), 28.6 (d), 27.1, 26.9 (q), 23.7 (t), 22.0, 21.9 (q), 15.5, 15.1 (d), 13.3, 13.2 (q), 12.6 (q), 12.2, 11.3 (t) ppm. GC/MS (EI): 234 (M+, 1), 192 (2), 174 (45), 159 (35), 145 (100), 129 (47), 113 (71), 91 (70), 77 (52), 53 (26), 43 (67). IR (neat, ν/cm-1): 2965, 2936,

2875, 1748, 1462, 1368, 1240, 1136. HRMS (EI): m/z: calcd. for $C_{15}H_{22}O_2$ 234.1620; found: 234.1609.

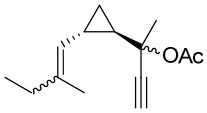
***rac*-(*E*)-2-(2-(pent-1-enyl)cyclopropyl)but-3-yn-2-yl acetate (1c)**



1c

Purified by distillation under reduced pressure to give a colourless liquid. Yield 70%. B. p. 110-115 °C/0.08 mbar. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.50 (ddd, J = 6.8, 6.8, 15.3 Hz, 1H), 5.05 (dd, J = 8.1, 15.3 Hz, 1H), 2.49 (s, 1H), 2.03 (s, 3H), 1.94 (dt, J = 6.8, 6.8 Hz, 2H), 1.75 (s, 3H), 1.58-1.49 (m, 1H), 1.39-1.29 (m, 3H), 1.10 (ddd, J = 5.3, 5.3, 8.5 Hz, 1H), 0.87 (t, J = 7.3 Hz, 3H), 0.63 (ddd, J = 5.3, 5.3, 8.5 Hz, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.2 (s), 131.3 (d), 129.5 (d), 81.1 (s), 76.8 (s), 73.9 (d), 34.5 (t), 28.3 (d), 27.1 (q), 22.6 (t), 21.9 (q), 18.7 (d), 13.6 (q), 11.5 (t) ppm. IR (neat, ν/cm-1): 2960, 2932, 1748, 1457, 1240, 1171, 1075, 1014. HRMS (EI): m/z: calcd. for $C_{14}H_{20}O_2$ 220.1463; found: 220.1448.

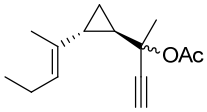
***rac*-2-(2-(2-Methylbut-1-enyl)cyclopropyl)but-3-yn-2-yl acetate (1d).**



1d

Purified by distillation under reduced pressure to give a colourless liquid. Yield 85%. B. p. 120-125 °C/0.08 mbar. 4 Isomers in a ratio of 4:2:2:1. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.64-4.57 (m, 1H), 2.52-2.51 (m, 1H), 2.26-1.61 (m, 9H), 2.04 (s, 3H), 1.35-1.25 (m, 1H), 1.91-1.11 (m, 1H), 1.06 -0.95 (m, 3H), 0.62-0.51 (m, 1H) ppm. 13C-NMR (75 MHz, $CDCl_3$): δ = 169.2 (s), 137.7, 137.6, 137.4 (s), 125.9, 125.8, 124.7, 124.5 (d), 81.3 (s), 76.0, 76.8, 76.7 (s), 73.9, 73.8 (d), 32.0, 25.3 (t), 28.6, 28.5 (d), 27.2, 27.1, 27.0 (q), 22.0 (q), 22.6, 16.4 (q), 15.8, 15.5, 15.4, 15.1 (d), 12.8, 12.7, 12.5 (q), 12.2, 12.1, 11.1 (t) ppm.GC/MS (EI): 220 (M+, 1), 178 (2), 160 (17), 145 (45), 131 (38), 115 (25), 99 (61), 81 (70), 67 (20), 53 (24), 43 (100). IR (neat, ν/cm- 1): 2966, 2936, 1748, 1457, 1369, 1240, 1176, 1014. HRMS (EI): m/z: calcd. for $C_{14}H_{20}O_2$ 220.1463; found: 220.1446.

***rac*-(*E*)-2-(2-(pent-2-en-2-yl)cyclopropyl)but-3-yn-2-yl acetate (1e)**

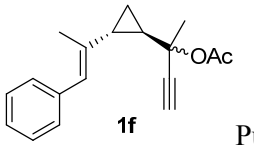


1e

Purified by distillation under reduced pressure to give a colourless liquid. Yield 82%. B. p. 120-122 °C/0.08 mbar. 2 Isomers in a ratio of 6:4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.21-5.14 (m, 1H), 2.51 (s, 1H), 2.04 (s, 3H), 2.04-1.94 (m, 2H), 1.77, 1.75 (2s, 3H), 1.58-1.58

(m, 4H), 1.39-1.32 (m, 1H), 1.04-0.93 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.83-0.72 (m, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.2 (s), 133.3, 133.0 (s), 126.1, 125.8 (d), 81.4 (s), 77.0, 76.8 (s), 73.9 (d), 27.2, 26.9 (d), 27.1, 26.8 (q), 24.2, 23.8 (d), 22.0 (q), 21.1, 21.0 (t), 15.1, 14.8 (q), 14.2 (q), 9.3, 8.3 (t) ppm. GC/MS (EI): 220 (M+, 1), 178 (4), 160 (36), 145 (82), 131 (62), 115 (33), 99 (69), 91 (61), 81 (67), 67 (15), 53 (22), 43 (100). IR (neat, ν/cm-1): 2963, 2935, 2873, 1748, 1455, 1369, 1241, 1170, 1076, 1014. HRMS (EI): m/z: calcd. for $C_{14}H_{20}O_2$ 220.1463; found: 220.1470.

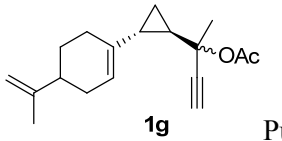
rac-(_E_)-2-(2'-(1-(Phenylprop-1-en-2-yl)cyclopropyl)but-3-yn-2yl acetate (1f)



1f

Purified by distillation under reduced pressure to give a colourless liquid. Yield 75%. B. p. 165- 175°C/0.08 mbar. 2 Isomers in a ratio of 1:1. ^{1}H-NMR (300 MHz, $CDCl^3$): δ = 7.33-7.15 (m, 5H), 6.33-6.31 (m, 1H), 2.55, 2.54 (s, 1H), 2.06 (s, 3H), 1.97-1.50 (m, 8H), 1.82-0.91 (m, 2H) ppm. ^{13}C-NMR (75 MHz, CDCl3): δ = 169.2 (s), 138.2, 138.1, 137.7, 137.5 (2s), 128.8 (2d), 128.1 (2d), 126.0 (d), 124.5, 124.3 (d), 81.3 (s), 76.8, 76.6 (s), 74.3, 74.2 (d), 27.7, 27.5 (d), 27.3, 27.0 (q), 25.4, 24.9 (d), 22.0 (q), 16.7, 16.5 (q), 10.1, 9.1 (t) ppm. GC/MS (EI): 268 (M+, 1), 226 (2), 208 (20), 193 (34), 178 (41), 165 (15), 147 (44), 129 (100), 115 (30), 91 (23), 77 (13), 65 (6), 43 (35). IR (neat, ν/cm-1): 3286, 3021, 2938, 1746, 1442, 1368, 1240, 1076. HRMS (EI): m/z: calcd. for $C_{18}H_{20}O_2$ 268.1463; found: 268.1472.

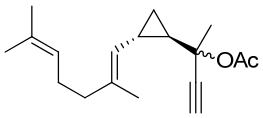
2-(2'-(4"-(Prop-1-en-2-yl)cyclohex-1"-enyl)cyclopropyl)but-3-yn-2-yl acetate (1g)



1g

Purified by distillation under reduced pressure to give a colourless liquid. Yield 65 %. B. p. 175-180 °C/0.10 mbar. 2 Main isomers in a ratio of 6:4. ^{1}H-NMR (300 MHz, $CDCl^3$): δ = 5.52-5.39 (m, 1H), 4.72-4.68 (m, 2H), 2.51 (s, 1H), 2.12-1.59 (m, 13H), 2.04 (s, 3H), 1.53- 1.31 (m, 2H), 1.04-0.67 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.3 (s), 150.0, 149.9 (s), 136.4, 136.1 (s), 120.2, 119.9 (d), 108.5 (t), 81.4, 81.3 (s), 76.8 (s), 73.9 (d), 41.2 (d), 30.6 (t), 27.7 (2t), 27.1 (q), 26.8, 26.6 (d), 22.6, 22.1 (d), 22.0 (q), 20.8 (q), 9.6, 8.6 (t) ppm. GC/MS (EI): 272 (M+, 1), 230 (2), 212 (22), 197 (19), 183 (6), 169 (44), 151 (72), 143 (35), 129 (96), 115 (44), 105 (57), 91 (92), 79 (56), 65 (19), 53 (25), 43 (100). IR (neat, ν/cm- 1): 2921, 1748, 1437, 1369, 1240, 1075, 1014, 889. HRMS (EI): m/z: calcd. for $C_{18}H_{24}O_2$ 272.1776; found: 272.1782.

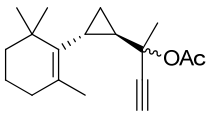
***rac*-2-(2'-(2,6-Dimethylhepta-1,5-dienyl)cyclopropyl)bu-3-yn-2-yl acetate (1h)**



1h

Purified by distillation under reduced pressure to give a colourless liquid. Yield 55%. B. p. 155-160 °C/0.10 mbar. 2 Main isomers in a ratio of 6:4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.22-5.06 (m, 1H), 4.65-4.62 (m, 1H), 2.52, 2.51 (s, 1H), 2.16-1.60 (m, 16H), 2.04 (s, 3H), 1.33-1.27 (m, 1H), 1.19-1.13 (m, 1H), 0.98-0.92, 0.62-0.51 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.3 (s), 135.6, 135.4 (s), 131.4, 131.3 (s), 126.1, 125.9 (d), 124.2, 124.1 (d), 81.3, 81.2 (s), 76.9, 76.7 (s), 73.9, 73.8 (d), 39.4 (t), 28.6 (d), 27.2 (q), 26.6 (t), 25.6 (q), 22.0 (q), 17.7 (q), 16.5 (q), 15.87, 15.38 (d), 12.16, 11.1 (t) ppm. GC/MS (EI): 274 (M+, 1), 214 (10), 195 (4), 171 (10), 153 (9), 145 (32), 135 (32), 115 (22), 105 (38), 91 (35), 69 (100), 53 (18), 41 (57). IR (neat, ν/cm-1): 2968, 2918, 1748, 1447, 1368, 1240, 1075, 1014. HRMS (EI): m/z: calcd. for $C_{18}H_{26}O_2$ 274.1933; found: 274.1913.

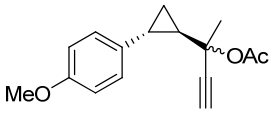
***rac*-2-(2'-(-2,6,6-Trimethylcyclohex-1-enyl)cyclopropyl)but-3-yn-2-yl acetate (1i)**



1i

Purified by distillation under reduced pressure to give a colourless liquid. Yield 65%. B. p. 155-160 °C/0.04 mbar. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.55 (s, 1H), 2.04 (s, 3H), 1.95-1.89 (m, 2H), 1.80 (s, 3H), 1.71 (s, 3H), 1.69-1.51 (m, 4H), 1.41-1.34 (m, 2H), 1.12 (s, 3H), 1.11 (s, 3H), 0.95 (ddd, J = 4.6, 4.9, 9.0 Hz, 1H), 0,71 (ddd, J = 4.7, 6.3, 9.0 Hz, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.3 (s), 135.3 (s), 130.4 (s), 82.3 (s), 77.1 (s), 73.8 (d), 41.7 (t), 35.5 (s), 33.8 (t), 29.1 (q), 28.7 (q), 26.9 (d), 26.0 (q), 22.0 (q), 21.0 (q), 19.2 (t), 17.7 (d), 11.4 (t) ppm. GC/MS (EI): 274 (M+, 1), 214 (25), 199 (54), 171 (17), 153 (69), 143 (100), 135 (98), 122 (44), 107 (98), 91 (98), 77 (71), 69 (25), 55 (29), 43 (79). IR (neat, ν/cm-1): 2929, 1746, 1459, 1368, 1241, 1073, 734. HRMS (EI): m/z: calcd. for $C_{18}H_{26}O_2$ 274.1933; found: 274.1930.

***rac*-2-(2-(*p*-Methoxy)cyclopropyl)but-3-yn-2-yl acetate (1j)**

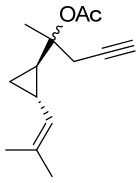


1i

A solution of trimethylsilyl acetylene (0.4 mL, 2.7 mmol) in THF (4 mL) was cooled to -78ºC and BuLi (1.6 M in hexanes, 1.6 mL, 2.6 mmol) was added dropwise. After 1h, a solution of **22j** (0.5 g, 2.6 mmol) in THF (2 mL) was added and the reaction was warmed up to room temperature overnight. The reaction was then diluted with MeOH (3 mL) and K_2CO_3 (1.0 g, 6.5 mmol) was added. The mixture was stirred at room temperature for 3 h, filtered over a path

of celite and rotavaped under reduced pressure. The residue was diluted with brine and extracted with dichloromethane, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Hexane/EtOAc = 100:1 to 20:1) to give propargylic alcohol as a colorless oil (0.35 g, 60% over 2 steps) which was subjected to the general procedure III.4) for acetylation affording **1j** as a colorless oil (0.18 g, 42%) as a mixture of isomers 3:1. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.06-7.03 (m, 2H, major and minor), 6.82- 6.78 (m, 2H, major and minor), 3.76 (s, 3H, OCH_3, major and minor), 2.58 (s, 1H, major), 2.59 (s, 1H, minor), 2.32-2.21 (m, 1H, major and minor), 2.01 (s, 3H, $COCH_3$, minor), 1.99 (s, 3H, $COCH_3$, major), 1.78 (s, 3H, CH_3, minor), 1.76 (s, 3H, CH_3, major), 1.59-1.54 (m, 1H, minor), 1.54-1.49 (m, 1H, major), 1.35-1.30 (m, 1H, minor), 1.17-1.08 (m, 1H, major and minor), 0.97-0.90 (m, 1H, major) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major and minor): δ = 168.9 (2 x C), 158.0, 157.9, 133.9, 133.8, 127.3, 127.2, 113.7, 113.6, 81.3, 81.1, 76.4, 76.1, 73.9, 73.8, 55.2 (2 x C), 30.4, 30.2, 26.9, 26.8, 21.6 (2 x C), 20.4, 19.5, 12.6, 11.4 ppm. ESIMS (M+ + Na): 281.1. IR (neat, ν/cm-1): 2982, 1514, 1462, 1244, 1177, 1034, 825. HRMS (EI): m/z: calcd. for $C_{16}H_{18}O_3Na$ 281.1154; found: 281.1157.

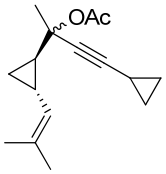
***rac*-2-(2-(2-Methylprop-1-enyl)cyclopropyl)pent-4-yn-2-yl acetate (13)**



13 A mixture of aluminum (93 mg, 3.45 mmol) and $HgCl_2$ (2.5 mg, 0.02 mmol) in THF (1.5 mL) was vigorously stirred for 1 h at room temperature. A solution of propargyl bromide (0.4 mL, 3.45 mmol) in THF (2.5 mL) was added dropwise over 1 hour. After stirring for 1 h at 25ºC, the mixture was cannulated to a solution of **22a** (0.19 g, 1.15 mmol) in THF (4 mL) at -78ºC. After 5 minutes, the reaction was quenched with a saturated solution of NH_4Cl, extracted with Et_2O, and dried over $MgSO_4$. The crude was used as such for the next acetylation step according to general procedure III.4) affording compound **13** as a colorless oil (0.14 g, 53%). Mixture of isomers: 1.5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61-4.58 (m, 1H, major and minor), 3.11-2.74 (m, 2H, major and minor), 2.35 (s, 1H, major), 2.34 (s, 1H, minor), 1.99 (s, 3H, $COCH_3$, major), 1.98 (s, 3H, $COCH_3$, minor), 1.72-1.64 (m, 6H, major and minor), 1.58-1.49 (m, 1H, major and minor), 1.38 (s, 3H, CH_3, major), 1.37 (s, 3H, CH_3, minor), 0.98-0.93 (m, 1H, major and minor), 0.84-0.87 (m, 1H, major), 0.59-0.53 (m, 1H, minor), 0.52-0.45 (m, 1H, major and minor) ppm. ^{13}C NMR (100 MHz, CDCl3): δ = 170.71, 170.69, 131.81, 131.70, 127.47, 127.37, 81.82, 81.79, 80.70, 80.68, 70.90, 70.89, 29.86, 29.77, 28.56, 28.54, 26.01, 26.00, 22.69 (2 x C), 22.25, 22.16, 18.68, 18.66, 15.47, 15.10, 11.26, 11.06 ppm. MS (EI): 220 (M+), 160 (8), 145 (36), 130 (11),

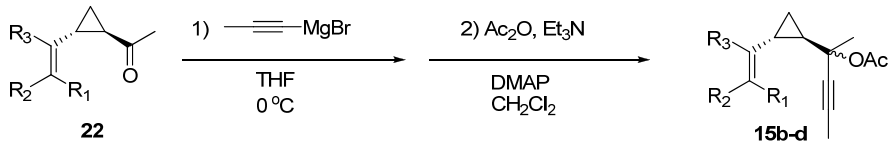
127 (16), 105 (22), 91 (26), 85 (48), 82 (90), 43 (100). IR (neat, ν/cm-1): 3298, 2971, 2365, 1733, 1367, 1241, 1078, 623. HRMS (EI): m/z: calcd. for $C_{14}H_{20}O_2$ 220.1463; found: 220.1464.

***rac*-4-Cyclopropyl-2-(2-(2-methylprop-1-enyl)cyclopropyl)but-3-yn-2-yl acetate (15a)**



15a According to steps 3) and 4) of general procedure for preparation of compounds **22**. The only difference is using cyclopropylacetylene instead of acetylene. Purified by distillation under reduced pressure to give a colourless liquid. Yield 40%. B. p. 125-130 °C/0.10 mbar. 2 Isomers in a ratio of 6:4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.63 (d, J = 8.5 Hz, 1H), 2.01, 2.00 (s, 3H), 1.75-1.67 (m, 9H), 1.60-1.50, 1.10-1.04 (m, 1H), 1.31-1.20 (m, 2H), 0.88-0.63 (m, 5H), 0.55-0.45 (m, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.9 (s), 132.3, 132.1 (s), 127.1, 127.0 (d), 90.3, 90.2 (s), 78.6, 78.5 (s), 73.2 (s), 29.3 (q), 28.2, 28.0 (d), 26.1 (q), 22.8 (q), 18.8 (q), 16.5, 16.3 (d), 12.6, 11.7 (t), 9.0 (2t), 0.0 (d) ppm. GC/MS (EI): 246 (M+, 1), 204 (2), 186 (25), 171 (43), 156 (25), 143 (90), 128 (100), 115 (54), 105 (28), 91 (67), 77 (49), 65 (25), 53 (20), 43 (56). IR (neat, ν/cm-1): 3008, 2977, 2923, 1745, 1445, 1367, 1242, 1071. HRMS (EI): m/z: calcd. for $C_{16}H_{22}O_2$ 246.1620; found: 246.1620.

General experimental procedure for the preparation of Compounds 15b-d.

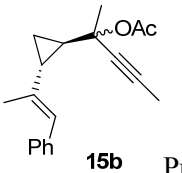


1) 1-Propynylmagnesium bromide (24 mL, 0.5 M in THF, 12 mmol) was was added dropwise to the corresponding cyclopropylmethyl ketones **22** (10 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at RT for 2 hours until completion of the reaction. Sat. NH_4Cl (100 mL) was added and the mixture was extracted 3 times with MTBE (100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated in vacuo to give the crude propargylic alcohol of larger than 95% purity (GC). This material was directly used in the next step.

2) Acetic anhydride (4.8 mL, 50 mmol) was added to a solution of the propargylic alcohol (10 mmol), Et_3N (14 mL, 100 mmol) and DMAP (0.12g, 1.0 mmol) in anhydrous CH_2Cl_2 (50 mL) at

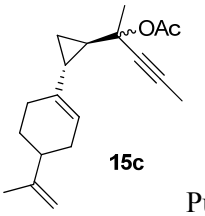
0 °C. The reaction was stirred at room temperature for 24 h, was concentrated and partitioned between MTBE and water. The organic layer was washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled bulb to bulb to give the desired acetate **15b-d.**

***rac*-1-Methyl-1-[2-(1-methyl-2-phenyl-vinyl)-cyclopropyl]-but-2-ynyl acetate (15b)**



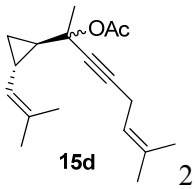
15b Purified by distillation under reduced pressure to give a colourless liquid. Yield 45%. B. p. 185-195 °C/0.07 mbar. 2 Isomers in a ratio of 3:2 ^{1}H-NMR (300 MHz, $CDCl^3$): δ = 7.38-7.15 (m, 5H; Ar-H), 6.32, 6.30 (2s, 1H), 2.03 (s, 3H), 1.86 (s, 3H), 1.83, 1.80 (2s, 3H), 1.78, 1.77 (2s, 3H), 1.74-1.62 (m, 1H), 1.59-1.50 (m, 1H), 1.15-0.87 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl^3$): δ = 169.4 (s), 138.3, 138.2 (s), 138.1, 137.8 (s), 128.8 (2d), 128.0 (2d), 125.9 (d), 124.3, 124.1 (d), 82.2, 82.1 (s), 78.1, 77.8 (s), 76.8, 76.7 (s), 28.0, 27.8 (d), 27.6, 27.3 (q), 25.4, 25.0 (d), 22.2 (q), 16.7, 16.5 (q), 10.0, 9.2 (t), 3.6 (q) ppm. GC/MS (EI): 282 (M+, 1), 240 (4), 222 (44), 207 (44), 192 (58), 178 (22), 165 (25), 147 (63), 129 (100), 115 (46), 105 (15), 91 (53), 77 (26), 65 (17), 55 (13), 43 (57). IR (neat, ν/cm-1): 2982, 2919, 1742, 1494, 1442, 1368, 1239, 1073, 699. HRMS (EI): m/z: calcd. for $C_{19}H_{22}O_2$ 282.1620; found: 282.1619.

2-(2'-(4"-(Prop-1-en-2-yl)cyclohex-1"-enyl)cyclopropyl)pent-3-yn-2-yl acetate (15c)



15c Purified by distillation under reduced pressure to give a colourless liquid. Yield 45%. B. p. 165-177 °C/0.06 mbar. 2 Isomers in a ratio of 6:4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.51-5.38 (m, 1H), 4.73-4.68 (m, 2H), 2.12-1.61 (m, 7H), 2.02 (s, 3H), 1.83 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.53-1.32 (m, 2H), 1.01-0.65 (m, 2H) ppm. Major isomer: ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.3 (s), 150.0, 149.9 (s), 136.6, 136.4 (s), 119.9, 119.6 (d), 108.4 (t), 81.9, 81.8 (s), 78.1, 78.0 (s), 76.8 (s), 41.2 (d), 30.6 (t), 27.9 (t), 27.8 (t), 27.4 (q), 27.2, 26.9 (d), 22.5, 22.2 (d), 22.1 (q), 20.7 (q), 9.6, 8.7 (t), 3.5 (q) ppm. GC/MS (EI): 286 (M+, 1), 244 (2), 226 (44), 211 (29), 197 (7), 183 (44), 169 (19), 151 (54), 143 (100), 128 (84), 115 (44), 105 (45), 91 (88), 77 (51), 67 (25), 53 (20), 43 (68). IR (neat, ν/cm-1): 2920, 1741, 1437, 1369, 1239, 1073, 889. HRMS (EI): m/z: calcd. for $C_{19}H_{26}O_2$ 286.1933; found: 286.1932.

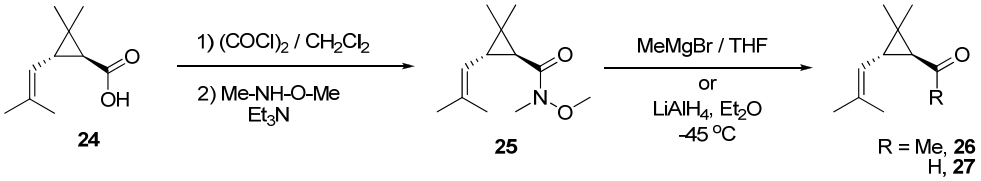
7-Methyl-2-((1R,2S)-2-(2-methylprop-1-enyl)cyclopropyl)oct-6-en-3-yn-2-yl acetate (15d)



15d

2 Isomers in a ratio of 1:4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.25-5.12 (m, 1H), 4.67-4.60 (m, 1H), 2.95 (d, *J*=6.0 Hz, 2H), 2.01, 2.00 (s, 3H), 1.85-1.81 (m, 1H), 1.75-1.67 (m, 12H), 1.35-0.85 (m, 5H), 0.55-0.45 (m, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.4, 169.3 (s), 133.8, 133.7 (s), 131.6, 131.4 (s), 126.6, 126.4 (d), 118.8, 118.7 (d), 85.2, 85.1 (s), 79.3, 79.1 (s), 78.1 (s), 29.4 (q), 28.7 (d), 27.6, 27.3 (q), 25.5, 25.4 (q), 25.3 (q), 22.2 (q), 18.1 (q), 17.8 (t), 15.9, 15.8 (d), 11.9, 11.2 (t) ppm. IR (neat, ν/cm-1): 2974, 2921, 1736, 1448, 1375, 1242, 1018. HRMS (EI): m/z: calcd. for $C_{18}H_{26}O_2$ 274.1933; found: 274.1933.

Preparation of 1k, (1*S*,3*S*)-1k, 15e and (1*S*,3*S*)-15e:



Oxalyl dichloride (12.7 g, 0.10 mol) was added dropwise to a solution of *rac-trans*-Chrysanthemic acid **24** or (1*S*,3*S*)-Chrysanthemic acid[5] (1*S*,3*S*)-**24** (16.8 g, 0.10 mol, 99%ee) in dichloromethane (100 mL) containing 1mL of DMF at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. Following that, a mixture of *N*-methoxymethanamine (12.2 g, 0.20 mol) and triethylamine (20.2 g, 0.20 mol) in dichloromethane (50 mL) was added dropwise. The mixture was stirred at RT for 2 hours. The solid was filtered off, the filtrate was concentrated and dissolved in MTBE (100 mL), washed once with water and then dried .

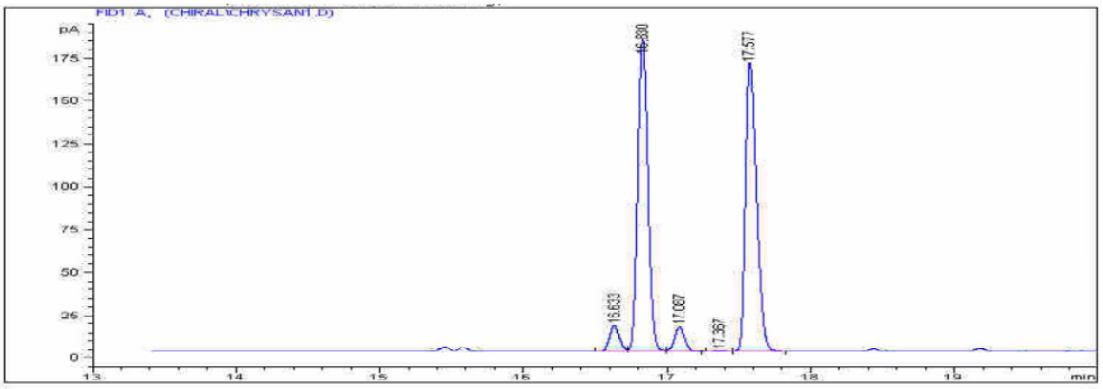
Distillation yielded 13.7 g (65%) of amide **25** as a colorless liquid. B. p. 125-130 °C/0.07 mbar ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.93 (d, *J* = 7.7 Hz, 1H), 3.69 (s, 3H), 3.21 (s, 3H), 2.15 (dd, *J* = 5.3, 7.7 Hz, 1H), 1.84 (d, *J* = 5.3 Hz, 1H), 1.71 (s, 6H), 1.19 (s, 3H), 1.17 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (s), 134.9 (s), 121.6 (d), 61.4 (q), 33.1 (d), 32.7 (q), 30.3 (d), 27.8 (s), 25.5 (q), 22.3 (q), 20.4 (q), 18.5 (q) ppm. GC/MS (EI): 211 (M+, 10), 196 (6), 180 (3), 151 (31), 123 (100), 109 (12), 91 (16), 81 (71), 67 (16), 55 (14), 41 (22). IR (neat, ν/cm-1): 2935, 1656, 1441, 1379, 1179, 1113. HRMS (EI): m/z: calcd. for $C_{12}H_{21}NO_2$ 211.1572; found: 211.1565. (1*S*,3*S*)-**25** $[\alpha]^{22}$ = -0.2 (*c* = 1.04, $CHCl_3$)**.**

***rac-trans*-1-(-2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)ethanone (26)**.[6] To a solution of **25** (10.5 g, 0.050 mol) in THF (50 mL) at 0 °C was added methyl magnesium bromide (2.0 M

in THF, 30 mL, 0.060 mol) dropwise. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched by addition of 1 N HCl and extracted with MTBE (150 mL). The organic layer was washed with brine and dried ($MgSO_4$). The crude product was purified by distillation to give **26** (4.1 g, yield 50%) as a colorless liquid. The analytical results were in accordance with the reference data. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.91 (d, *J* = 7.9 Hz, 1H, $(CH_3)_2C$=C*H*-), 2.22 (s, 3H, $COCH_3$), 2.23-2.17 (m, 1H), 1.73 (d, *J* = 5.4 Hz, 1H), 1.71 (s, 3H, $(CH_3)_2C$=C), 1.68 (s, 3H, $(CH_3)_2C$=C), 1.30 (s, 3H, CH_3), 1.18 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.0 (s), 135.2 (s), 121.3 (d), 43.7 (d), 34.2 (d), 32.3 (q), 32.2 (q), 25.5 (q), 22.4 (q), 19.6 (q), 18.4 (q) ppm. GC/MS (EI): 166 (M+, 2), 151 (3), 123 (100), 108 (4), 95 (12), 81 (65), 67 (14), 55 (10), 43 (36). IR (neat, ν/cm-1): 2925, 1695, 1415, 1377, 1360, 1194, 1172, 1113, 952, 848.

(1*S*,3*S*)-*trans*-1-(-2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)ethanone (**(1*S*,3*S*)-26**). This compound was prepared from (1*S*,3*S*)-**25** in an analogous way. 99% ee. $[\alpha]^{22}$ = -55.7 (c = 0.96, $CHCl_3$). The enantiomeric excess of **26** was determined by GC with a chiral MN HYDRODEX-beta-6TBDM column.

GC chromatogram of *rac*-(**26**)



Area Percent Report

Sorted By : Signal
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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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2	16.830	VV	0.0771	888.86456	181.54767	46.15128
3	17.087	VB	0.0765	70.07009	14.46614	3.63015
4	17.367	BV	0.0782	1.77990	3.44694e-1	0.09242
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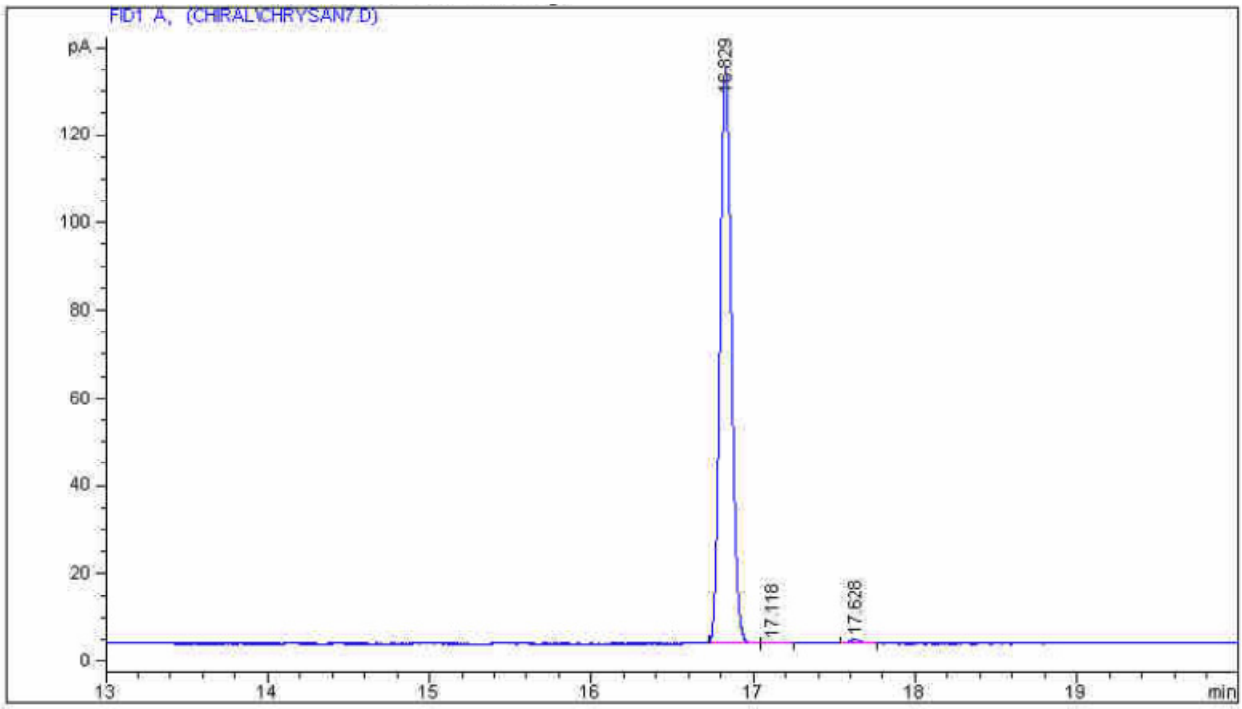
Totals :				1925.98032	379.41389	

GC chromatogram of (1S,3S)-(**26**)

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================================================================================
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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1  16.829 BB    0.0793  644.82837  131.30432 99.17781
   2  17.118 BB    0.0948    1.39148 2.06070e-1  0.21402
   3  17.628 BP    0.0744    3.95419 8.47383e-1  0.60817

Totals :                   650.17404  132.35777
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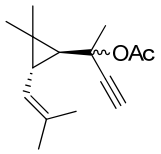
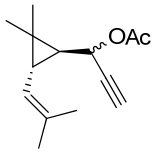
***rac*-2-(2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)but-3-yn-2-yl acetate (1k)**



1k From compound *rac*-**26** according to steps 3) and 4) of the procedure for preparation of compounds **23**. Purified by distillation under reduced pressure to give a colourless liquid. Yield 45%. B. p. 130-136 °C/0.08 mbar. 2 Isomers in a ratio of 3:1. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.92-4.87 (m, 1H), 2.61 (s, 1H), 2.02 (s, 3H), 1.82-1.76 (m, 1H), 1.74 (s, 3H), 1.72 (2s, 6H), 1.30 (s, 3H), 1.03 (s, 3H), 0.91 (d, J = 5.8 Hz, 1H) ppm. Major isomer: ^{13}CNMR (75 MHz, $CDCl_3$): δ = 169.3, 168.7 (s), 133.9 (s), 123.0 (d), 83.5 (s), 75.6 (s), 74.7, 74.6 (d), 41.9, 41.6 (d), 29.7, 29.3 (d), 27.9 (q), 27.8 (q), 25.5 (q), 23.8 (s), 22.7 (q), 21.9 (q), 20.5, 18.4 (q) ppm. GC/MS (EI): 234 (M+, 1), 192 (2), 174 (12), 159 (100), 144 (25), 129 (39), 117 (29), 105 (51), 91 (61), 65 (20), 53 (21), 43 (99). IR (neat, ν/cm-1): 2971, 1736, 1438, 1368, 1248, 1129. HRMS (EI): m/z: calcd. for $C_{15}H_{22}O_2$ 234.1620; found: 234.1626.

(1*S*,3*S*)-2-(2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)but-3-yn-2-yl acetate ((1*S*,3*S*)-1k). This compound was prepared from (1*S*,3*S*)-**26** in an analogous way. 99% ee. D.r = 6:4. $[\alpha]^{22}$ = -36.5 (c = 0.84, $CHCl_3$)**.**

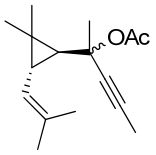
***rac*-2-(2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)prop-2-ynyl acetate (9)**



9 To a solution of amide **25** (4.22 g, 0.02 mol) in diethyl ether (30 mL) was added $LiAlH_4$ (0.760 g, 0.02 mol) in 4 portions under argon atmosphere at -45 ^{o}C . The reaction mixture was stirred at -45 ^{o}C for 30 min and quenched with 1 N HCl. The organic phase was separated and washed with brine, then dried ($MgSO_4$). The crude product was purified by distillation to give 2.13 g (yield 70%) of aldehyde **27** as a colorless liquid. The analytical results were in accordance to the reference data.[7] Preparation of **9** was performed according to steps 3) and 4) of the general procedure for preparation of compounds **22**. Purified by distillation under reduced pressure yielded **9** (80%) as a colourless liquid. B. p. 110-111 °C/0.09 mbar. 2 Isomers in a ratio of 1:1. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.14, 5.00 (2dd, J = 2.1, 10.0 Hz, 1H), 4.91, 4.85 (2 bd, J = 7.5 Hz, 1H), 251, 2.45 (2d, J = 2.1Hz, 1H), 2.10, 2.09 (2s, 3H), 1.72-1.66 (m, 6H), 1.39-0.96 (m, 8H) ppm. 13C-NMR (75 MHz, CDCl3): δ = 170.0, 169.7 (s), 134.6, 134.2 (s), 122.1, 121.9 (d), 81.5, 81.4 (s), 73.3, 72.6 (d), 65.1, 64.9 (d), 36.4, 36.3 (d), 29.8, 28.4 (d), 25.6 (q), 23.2, 22.6 (s), 22.3, 22.2, 21.8, 21.3, 21.1, 21.0 (3q), 18.4, 18.1 (q) ppm. GC/MS (EI): 220 (M+, 1), 178 (2), 160 (13),

145 (85), 123 (75), 106 (38), 91 (80), 81 (82), 67 (21), 53 (21), 43 (100). IR (neat, ν/cm-1): 2925, 1743, 1451, 1371, 1234, 1126, 1017. HRMS (EI): *m/z*: calcd. for $C_{14}H_{20}O_2$ 220.1463; found: 220.1467.

(1*S*,3*S*)-2-(2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)pent-3-yn-2-yl acetate (**15e**)

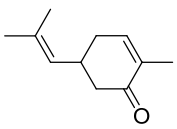


15e According to steps 1) and 2) of general procedure for preparation of compounds **15b-d.** Purified by distillation under reduced pressure to give a colourless liquid. Yield 35%. B. p. 125-132 °C/0.07 mbar. 2 Isomers in a ratio of 4:1. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.93-4.90 (m, 1H), 2.02 (s, 3H), 1.87 (s, 3H), 1.85 (s, 3H), 1.85-1.65 (m, 1H), 1.71 (s, 6H), 1.32 (s, 3H), 1.17 (d, *J* = 5.3 Hz, 1H), 1.01 (s, 3H), ppm. Major isomer: ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.5 (s), 133.5 (s), 123.3 (d), 83.6 (s), 79.2 (s), 78.8 (s), 41.9 (d), 30.0 (d), 29.6 (q), 25.5 (q), 24.0 (s), 23.4 (q), 22.2 (q), 20.9 (q), 18.4 (q), 3.52 (q) ppm. GC/MS (EI): 248 (M+, 1), 206 (2), 188 (10),173 (100), 158 (25), 143 (32), 131 (28), 119 (35), 105 (32), 91 (36), 77 (20), 67 (12), 53 (11), 43 (39). IR (neat, ν/cm-1): 2921, 1737, 1448, 1367, 1244, 1144, 1014. HRMS (EI): m/z: calcd. for $C_{16}H_{24}O_2$ 248.1776; found: 248.1779.

(1*S*,3*S*)-2-(2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)pent-3-yn-2-yl acetate ((1S,3S)-15e). This instable compound was prepared from (1*S*,3*S*)-**26** in an analogous way and cycloisomerized immediately. The analytical data are identical with those of *rac*-**15e**.

General procedure A for the 2-cyclohexenone synthesis:

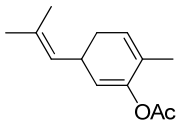
2-Methyl-5-(2-methylprop-1-enyl)cyclohex-2-enone (8a)



8a Methylene chloride (10 mL) was added to a mixture of gold complex [$AuCl(PPh_3)$] (49.4 mg, 0.10 mmol) and $AgSbF_6$ (34.3 mg, 0.10 mmol), and the reaction mixture was stirred for 10 min under argon atmosphere. The resulting solution was filtered through a pad of celite. A solution of **1a** (2.06 g, 10 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred for 2 min. Methanol (10 mL) and K_2CO_3 (2.76 g, 20 mmol) were added. The resulting mixture was stirred for 30 min and concentrated. The residue was neutralized with 1N HCl and extracted 3

times with MTBE (30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography on silica gel, eluent: hexane:MTBE (10:1) to yield **8a** (1.39 g, 85%) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78-6.68 (m, 1H, C*H*=C(CH_3)C=O), 5.05 (d, *J* = 8.4 Hz, 1H, C*H*=C(CH_3)$_2$), 3.05-2.86 (m, 1H, 5-H), 2.48-2.14 (m, 4H), 1.78 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.62 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8 (s), 144.8 (d), 135.5 (s), 132.7 (s), 127.1 (d), 44.7 (t), 35.1 (d), 32.8 (t), 25.7 (q), 17.8 (q), 15.8 (q) ppm. GC/MS (EI): 164 (M+, 34), 149 (5), 121 (5), 107 (6), 93 (5), 82 (100), 67 (11), 54 (16). IR (neat, ν/cm-1): 2965, 2876, 1676, 1455, 1432, 1244, 1138, 1101. HRMS (EI): *m/z*: calcd. for $C_{11}H_{16}O$ 164.1201: Found: 164.1192.

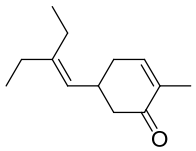
3-(2-Ethylbut-1-enyl)-6-methylcyclohexa-1,5-dienyl acetate (7a)



7a

In another example, the reaction mixture was concentrated prior methanolysis and the crude product was purified by distillation under reduced pressure to give compound **7a** as a colorless liquid. Yield 80%. B. p.: 115-122 °C/0.09 mbar. ^{1}H-NMR (300 MHz, $CDCl_3$): *δ* = 5.63-5.59 (m, 1H), 5.25-5.15 (m, 2H), 3.41-3.29 (m, 1H), 2.30-1.95 (m, 5H), 1.68 (s, 3H), 1.65 (s, 3H), 1.61 (s, 3H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$): *δ* = 169.5 (s), 146.7 (s), 131.9 (s), 129.0 (s), 126.4 (d), 124.0 (d), 116.8 (d), 32.8 (d), 29.5 (t), 25.6 (q), 20.6 (q), 17.8 (q), 16.6 (q) ppm. GC/MS (EI): 206 (M+, 12), 164 (100), 149 (48), 131 (12), 121 (71), 109 (49), 96 (46), 79 (16), 69 (15), 55 (11), 43 (26). IR (neat, ν/cm-1): 2967, 1757, 1460, 1370, 1214. HRMS (EI): *m/z*: calcd. for $C_{13}H_{18}O_2$ 206.1307: Found: 206.1311.

5-(2-Ethyl-but-1-enyl)-2-methyl-cyclohex-2-enone (8b)

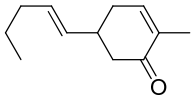


8b

Using general procedure A, a mixture of **1b** (2.34 g, 10 mmol) and gold complex Au(PPh_3)SbF_6 (0.10 mmol) were reacted and methanolyzed to give **8b** as a colorless liquid (1.50 g, 78 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75-6.68 (m, 1H, 3-H), 4.99 (d, *J* = 9.2 Hz, 1H), 3.06-2.93 (m, 1H, 5-H), 2.47-2.41 (m, 1H), 2.39-2.30 (m, 1H), 2.27-2.10 (m, 2H), 2.03 (q, *J* = 7.5 Hz, 2H, *CH*$_2$CH$_3$), 2.01 (q, *J* = 7.5 Hz, 2H, *CH*$_2$CH$_3$), 1.78 (s, 3H, 2-CH_3), 0.98 (t, *J* = 7.5 Hz, 3H, CH_2(*CH*$_3$)a), 0.96 (t, *J* = 7.5 Hz, 3H, CH_2(*CH*$_3$)b) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.7 (s), 144.7 (d), 144.1 (s), 135.5 (s), 125.2 (d), 45.1 (t), 34.7 (d), 33.2 (t), 28.9 (t), 23.4 (t), 15.7 (q), 13.7 (q), 12.7 (q) ppm. GC/MS (EI): 192 (M+, 21), 163 (11), 121 (15), 110 (53), 95 (22),

82 (100), 67 (5), 54 (17), 41 (18). IR (neat, ν/cm-1): 2965, 2934, 2876, 1676, 1460, 1366, 1243, 1103. HRMS (EI): m/z: calcd. for $C_{13}H_{20}O$ 192.1514; found: 192.1523.

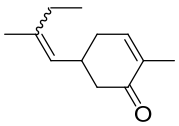
2-Methyl-5-((E)-pent-1-enyl)cyclohex-2-enone (**8c**)



8c

Using general procedure A, a mixture of **1c** (2.20 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **8c** as a colorless liquid (1.10 g, 62 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80-6.65 (m, 1H, 3-H), 5.52-5.35 (m, 2H), 2.84-2.65 (m, 1H, 5-H), 2.55-2.51 (m, 1H), 2.47-2.35 (m, 1H), 2.30-2.10 (m, 2H), 2.04-1.93 (m, 2H), 1.77 (s, 3H, 2-CH_3), 1.43-1.31 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H, CH_2*CH_3*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5 (s), 144.3 (d), 135.6 (s), 132.4 (d), 130.3 (d), 44.4 (t), 38.5 (d), 34.5 (t), 32.7 (t), 22.4 (t), 15.7 (q), 13.5 (q) ppm. GC/MS (EI): 178 (M+, 2), 149 (1), 134 (14), 122 (7), 107 (8), 93 (8), 82 (100), 67 (5), 54 (22), 39 (12). IR (neat, ν/cm-1): 2958, 2925, 2873, 1677, 1452, 1434, 1366, 1243, 969. HRMS (EI): m/z: calcd. for $C_{12}H_{18}O$ 178.1358; found: 178.1363.

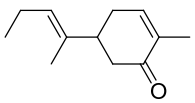
2-Methyl-5-(2-methyl-but-1-enyl)-cyclohex-2-enone (8d)



8d

Using general procedure A, a mixture of **1d** (2.20 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **8d** as a colorless liquid (1.46 g, 82 % yield). Mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77-6.68 (m, 1H, 3-H), 5.07-4.98 (m, 1H), 3.05-2.88 (m, 1H, 5-H), 2.49-2.40 (m, 1H), 2.39-2.27 (m, 1H), 2.26-2.06 (m, 2H), 2.03-1.94 (m, 2H), 1.78 (br s, 3H, 2-CH_3), 1.68, 1.62 (s, 3H, CH_3), 1.00-0.94 (m, 3H, CH_2*CH_3*) ppm. Major isomer: ^{13}C NMR (75 MHz, $CDCl_3$): δ =199.8 (s), 144.7 (d), 138.2 (s), 135.5 (s), 125.5 (d), 44.7 (t), 34.9 (d), 32.8 (t), 32.2 (t), 16.0 (q), 15.7 (q), 12.6 (q) ppm. GC/MS (EI): 178 (M+, 21), 163 (1), 149 (5), 122 (6), 107 (8), 96 (25), 82 (100), 67 (5), 54 (17), 41 (13). IR (neat, ν/cm-1): 2965, 2923, 1676, 1451, 1364, 1101, 902. HRMS (EI): m/z: calcd. for $C_{12}H_{18}O$ 178.1358; found: 178.1366.

2-Methyl-5-(1-methyl-but-1-enyl)-cyclohex-2-enone (8e)

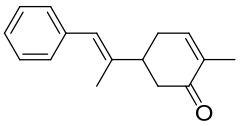


8e

Using genral procedure A, a mixture of **1e** (2.20 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **8e** as a colorless liquid (1.71

g, 96 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84-6.72 (m, 1H, 3-H), 5.20 (t, *J* = 6.9 Hz, 1H), 2.70-2.59 (m, 1H, 5-H), 2.50 (dd, *J* = 3.5, 15.9 Hz, 1H), 2.39-2.25 (m, 3H), 2.06-1.97 (m, 2H), 1.78 (s, 3H, 2-CH_3), 1.61 (s, 3H, CH_3), 0.95 (t, *J* = 7.5 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1 (s), 144.9 (d), 135.5 (s), 135.2 (s), 126.9 (d), 44.2 (d), 43.3 (t), 31.4 (t), 21.0 (t), 15.6 (q), 14.1 (q), 13.8 (q) ppm. GC/MS (EI): 178 (M+, 17), 163 (2), 149 (8), 134 (11), 121 (11), 107 (12), 82 (100), 54 (18), 41 (12). IR (neat, ν/cm-1): 2962, 1677, 1451, 1366, 1244, 1099. HRMS (EI): m/z: calcd. for $C_{12}H_{18}O$ 178.1358; found: 178.1358.

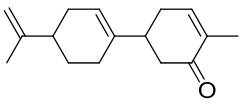
2-Methyl-5-(1-methyl-2-phenyl-vinyl)-cyclohex-2-enone (8f)



8f

Using general procedure A, a mixture of **1f** (2.68 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **8f** as a colorless oil (1.99 g, 88 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.18 (m, 5H, Ar-H), 6.87-6.77 (m, 1H), 6.34 (s, 1H), 2.92-2.78 (m, 1H), 2.68-2.60 (m, 1H), 2.53-2.40 (m, 3H), 1.86 (s, 3H, CH_3), 1.81 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =199.6 (s), 144.6 (d), 139.6 (s), 137.8 (s), 135.4 (s), 128.9 (d), 128.1 (d), 126.3 (d), 125.3 (d), 45.0 (d), 43.2 (t), 31.3 (t), 15.7 (2q) ppm. GC/MS (EI): 226 (M+, 29), 182 (10), 169 (7), 156 (4), 144 (39), 129 (100), 115 (16), 91 (20), 77 (7), 65 (5), 54 (8), 39 (9). IR (neat, ν/cm-1): 3023, 2921, 1674, 1493, 1448, 1366, 1107. HRMS (EI): m/z: calcd. for $C_{16}H_{18}O$ 226.1358; found: 226.1359.

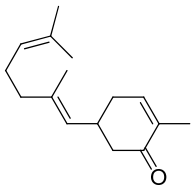
4'-Isopropenyl-4-methyl-bicyclohexyl-4,1'-dien-3-one (8g)



8g

Using general procedure A, a mixture of **1g** (2.72 g, 10 mmol), gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **8g** as a colorless oil (1.29 g, 56 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77-6.72 (m 1H), 5.55-5.45 (m, 1H), 4.71 (s, 2H), 2.70-2.45 (m, 2H), 2.44-2.22 (m, 3H), 2.21-1.85 (m, 6H), 1.78 (s, 3H, CH3), 1.74 (s, 3H, CH_3), 1.55-1.38 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0 (s), 149.7 (s), 144.8 (d), 138.6 (s), 135.3 (s), 120.9 (d), 108.6 (t), 43.4 (t), 42.5 (d), 41.0 (d), 31.4 (t), 30.6 (t), 27.7 (t), 26.8 (t), 20.7 (q), 15.7 (q) ppm. GC/MS (EI): 230 (M+, 18), 215 (3), 202 (4), 187 (29), 173 (6), 159 (10), 145 (25), 134 (26), 119 (20), 105 (57), 93 (45), 82 (100), 68 (27), 54 (24), 41 (24). IR (neat, ν/cm-1): 2922, 1675, 1435, 1367, 1099, 889. HRMS (EI): m/z: calcd. for $C_{16}H_{22}O$ 230.1671; found: 230.1672.

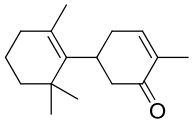
5-(2,6-Dimethyl-hepta-1,5-dienyl)-2-methyl-cyclohex-2-enone (8h)



8h

Using general procedure A, a mixture of **1h** (2.74 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **8h** as a colorless oil (1.65 g, 71 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75-6.68 (m, 1H), 5.10-5.03 (m, 2H), 3.04-2.88 (m, 1H), 2.45 (dd, *J* = 4.1, 16.2 Hz, 1H), 2.38-2.28 (m, 1H), 2.26-1.92 (m, 6H), 1.79 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.60 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =199.7 (s), 144.7 (d), 136.2 (s), 135.5 (s), 131.5 (s), 127.0 (d), 123.9 (d), 44.7 (t), 39.5 (t), 34.9 (d), 32.8 (t), 26.5 (t), 25.6 (q), 17.7 (q), 16.1 (q), 15.7 (q) ppm. GC/MS (EI): 232 (M+, 17), 164 (18), 149 (19), 135 (4), 121 (25), 109 (29), 93 (17), 82 (28), 69 (100), 55 (14), 41 (44). IR (neat, ν/cm-1): 2922, 1677, 1450, 1364, 1246. HRMS (EI): m/z: calcd. for $C_{16}H_{24}O$ 232.1827; found: 232.1830.

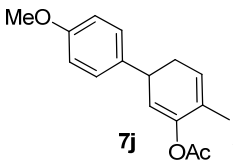
4,2',6',6'-Tetramethyl-bicyclohexyl-4,1'-dien-3-one (8i)



8i

Using general procedure A, a mixture of **1i** (2.74 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **8i** as a colorless oil (2.09 g, 90 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78-6.72 (m, 1H, 3-H), 2.94-2.83 (m, 2H), 2.82-2.68 (m, 1H), 2.43-2.36 (m, 1H), 2.32-2.18 (m, 1H), 1.92 (t, *J* = 6.1 Hz, 2H), 1.79 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.58-1.48 (m, 2H), 1.45-1.35 (m, 2H), 0.99 (s, 3H, CH_3), 0.98 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8 (s), 145.8 (d), 138.1 (s), 134.8 (s), 129.5 (s), 42.9 (t), 39.9 (t), 36.0 (s), 35.7 (d), 34.4 (t), 31.6 (t), 27.9 (q), 27.8 (q), 21.9 (q), 19.3 (t), 15.9 (q) ppm. GC/MS (EI): 232 (M+, 36), 217 (14), 175 (15), 161 (10), 150 (24), 135 (100), 123 (76), 109 (40), 91 (31), 79 (31), 55 (21), 41 (33). IR (neat, ν/cm-1): 2927, 2866, 1675, 1454, 1363, 1244, 1092. HRMS (EI): m/z: calcd. for $C_{16}H_{24}O$ 232.1827; found: 232.1827.

3-(*p*-Methoxyphenyl)-6-methylcyclohexa-1,5-dienyl acetate (7j)

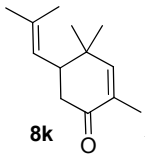


7j

Using general procedure A, a mixture of **1j** (0.10 g, 0.4 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.004 mmol) were reacted. In this example, the reaction mixture was

concentrated prior to methanolysis and the crude product was purified by column chromatography on silica gel, eluent: hexane:EtOAc (100:1) to yield **7j** (70 mg, 70%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24-7.22 (m, 2H), 6.85-6.29 (m, 2H), 5.57 (d, *J* = 1.5 Hz, 1H), 5.43 (d, *J* = 4.2 Hz, 1H), 3.78 (s, 3H, OCH_3), 3.70 (dc, *J* = 4.3, 9.2 Hz, 1H), 2.58-2.50 (m, 1H), 2.37-2.28 (m, 1H), 2.19 (s, 3H, $COCH_3$), 1.70 (d, 3H, *J* = 1.8 Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 158.4, 147.7, 136.3, 129.3, 128.5, 123.7, 116.6, 113.9, 55.4, 39.1, 32.6, 20.9, 16.8 ppm. MS (EI): 258.1 (M+, 9), 256 (29), 216 (62), 214 (87), 199 (31), 198 (13), 137 (32), 121 (100), 108 (19), 57 (11), 43 (17). IR (neat, ν/cm-1): 2953, 2917, 2849, 2836, 2355, 2343, 2337, 2327, 1758, 1609, 1511, 1367, 1245, 1215, 1123, 1036, 828. HRMS (EI): m/z: calcd. for $C_{16}H_{18}O_3$ 258.1256; found: 258.1250.

2,4,4-Trimethyl-5-(2-methyl-propenyl)-cyclohex-2-enone (8k)

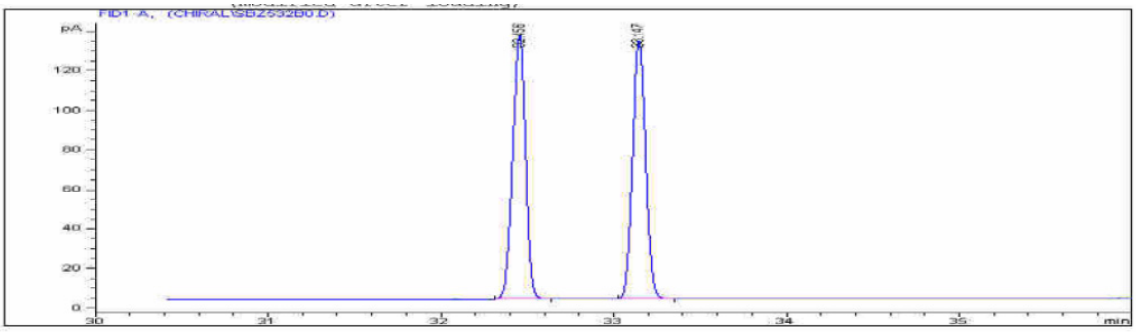


8k

Using general procedure A, a mixture of **1k** (2.34 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **8k** as a colorless oil (1.50 g, 78 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.43 (s, 1H, 3-H) 5.03 (d, *J* = 9.2 Hz, 1H), 2.77 (ddd, *J* = 10.5, 10.5, 9.2 Hz, 1H), 2.41-2.24 (m, 2H), 1.75 (s, 3H), 1.73 (s, 3H), 1.62 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0 (s), 156.1 (d), 133.6 (s), 132.3 (s), 123.9 (d), 43.0 (d), 40.7 (t), 36.9 (s), 28.2 (q), 26.0 (q), 20.9 (q), 18.2 (q), 15.7 (q) ppm. GC/MS (EI): 192 (M+, 16), 177 (1), 135 (2), 110 (100), 95 (43), 82 (16), 67 (40), 53 (5), 41 (14). IR (neat, ν/cm-1): 2966, 1677, 1448, 1368, 1269, 1086, 1016. HRMS (EI): m/z: calcd. for $C_{13}H_{20}O$ 192.1514; found: 192.1520.

(5*R*)-2,4,4-Trimethyl-5-(2-methyl-propenyl)-cyclohex-2-enone ((*R*)-8k). This compound was prepared from (1*S*,3*S*)-**1k** in an analogous way. 27% ee. $[\alpha]^{22}$ = +28.4 (*c* 0.58, $CHCl_3$).

GC chromatogram of *rac*-**8k**



Area Percent Report

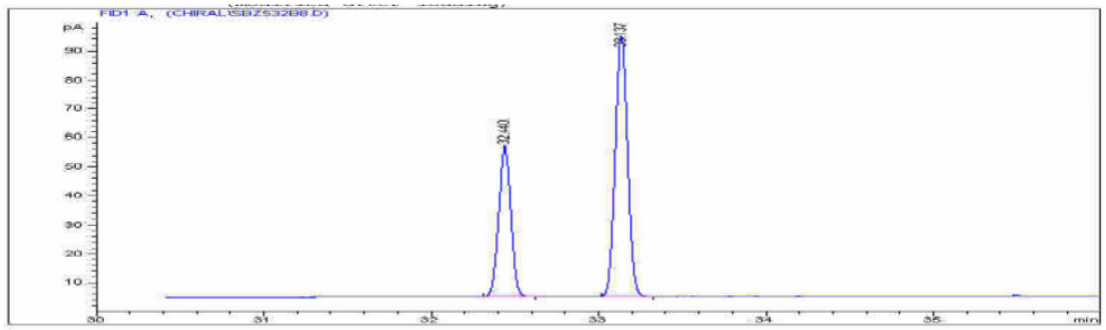
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.456	BB	0.0825	689.46545	132.93239	50.03483
2	33.147	BB	0.0821	688.50549	129.39760	49.96517

Totals : 1377.97095 262.32999

GC chromatogram of *(R)*-**8k** (27%ee) which was prepared by Au(I)



Area Percent Report

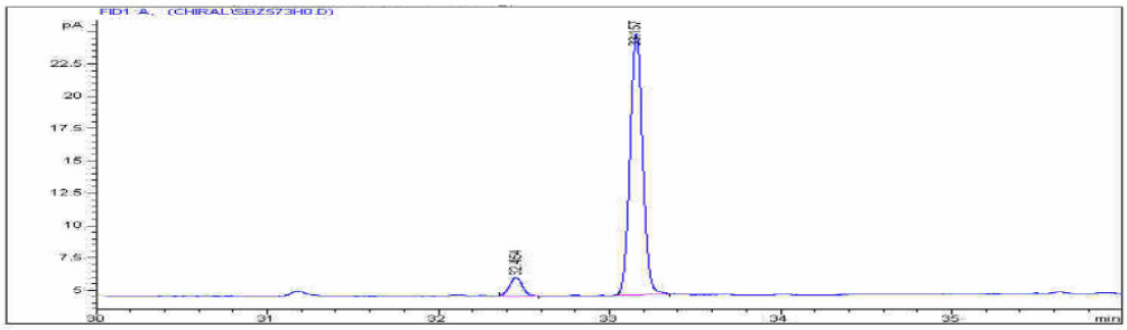
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.440	BB	0.0774	263.82357	51.83036	36.19938
2	33.137	BB	0.0824	464.98355	89.85049	63.80062

Totals : 728.80722 141.68085

GC chromatogram of *(R)*-**8k** (87%ee) which was prepared by Au(III)



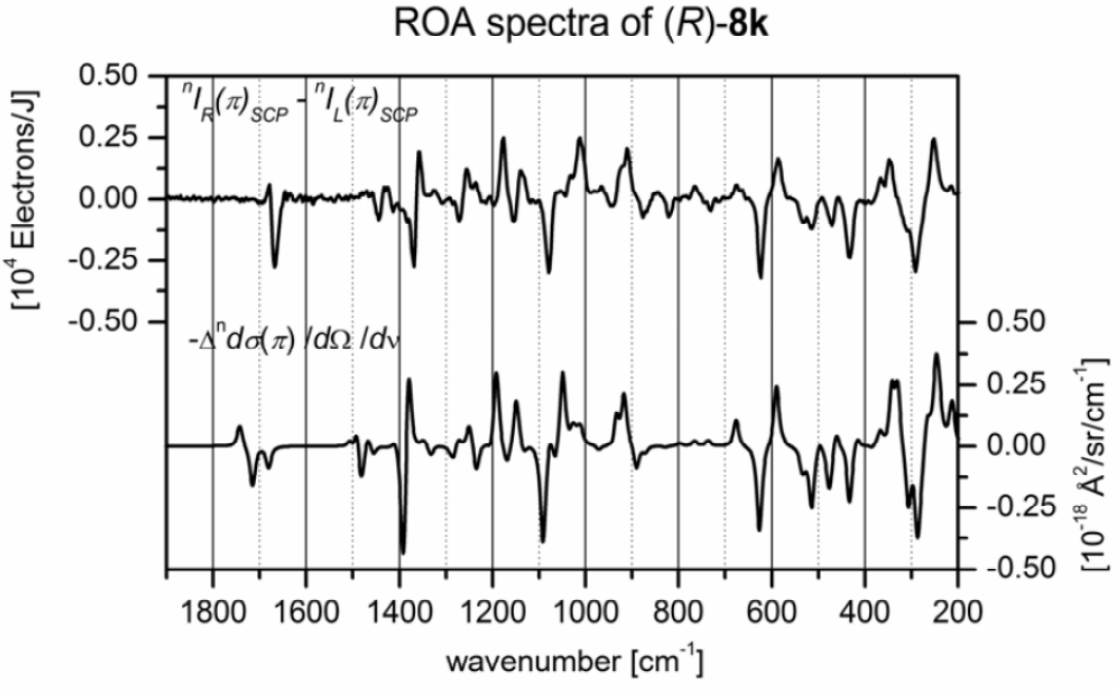
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

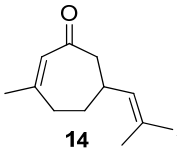
Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.454	BB	0.0794	7.02842	1.38037	6.36460
2	33.157	BB	0.0801	103.40153	20.07302	93.63540
Totals :				110.42995	21.45339	

The absolute configuration of (*R*)-**8k** was determined by comparing the vibrations of a measured ROA (Raman Optical Activity) spectra (below) with those of the theoretical spectra, calculated at the B97-1/pc-2 level with the Gaussian program (above).[1a,b,d] ROA calculations at the TDHF/DPS level was carried out with the Dalton program.[1c]



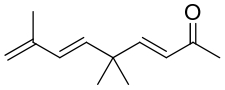
***rac*-3-Methyl-6-(2-methylprop-1-enyl)cyclohept-2-enone (14)**



14

Methylene chloride (18 ml) was added to a mixture of dichloro(pyridin-2-carboxylate)gold complex (17 mg, 0.045 mmol) and homopropargyl acetate **13** (0.20 g, 0.91 mmol) and the reaction mixture was stirred for 15 min. under argon atmosphere. The resulting solution was diluted with MeOH (18 ml) and K_2CO_3 (251 mg, 1.82 mmmol) was added and stirred at room temperature for 90 minutes. The resulting solution was quenched with water and the aquous layer was extracted with dichloromethane several times. The organic layers were dried over Na_2SO_4 anhydrous. The residue was purified by column chromatography on silica gel, eluent: hexane:EtOAc (100:1) to yield **14** (0.140 g, 72%) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (s, 1H), 5.06 (dd, *J* = 1.1, 9.3 Hz, 1H), 2.84-2.75 (m, 1H), 2.63 (dd, *J* = 5.0, 14 Hz, 1H), 2.53-2.45 (m, 2H), 2.33 (ddd, *J* = 3.0, 8.4, 17 Hz, 1H), 1.95 (s, 3H, CH_3), 1.93-1.87 (m, 1H), 1.66 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.62-1.54 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3 (s), 159.5 (s), 131.2 (s), 129.9 (d), 128.0 (d), 49.0 (t), 33.1 (t), 33.0 (t), 32.3 (d), 27.5 (q), 25.6 (q), 17.8 (q) ppm. MS (EI): 178 (M+, 5), 163 (5), 145 (5), 135 (17), 121 (18), 107 (31), 95 (32), 93 (100), 80 (64), 82 (50), 67 (44), 41 (39). IR (neat, ν/cm-1): 2967, 2924, 2859, 1655, 1440, 1375, 1273, 1258, 1100, 1021, 835. HRMS (EI): m/z: calcd. for $C_{12}H_{18}O$ 178.1358; found: 178.1355.

(3*E*,6*E*)-5,5,8-Trimethylnona-3,6,8-trien-2-one (10)[2]

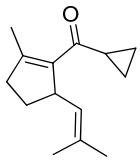


10

A mixture of **9** (2.34 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) in 1,2-DCE were refluxed for 1 hour and methanolyzed to give **10** as a colorless oil (0.354 g, 20 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75 (d, *J* = 16.2 Hz, 1H, 4-H), 6.11 (d, *J* = 16.1 Hz, 1H, 7-H), 6.02 (d, *J* = 16.2 Hz, 1H, 3-H), 5.60 (d, *J* = 16.1 Hz, 1H, 6-H), 4.95 (2s, 2H, 9-H), 2.27 (s, 3H, $COCH_3$), 1.84 (s, 3H, 8-CH_3), 1.23 (s, 6H, 5-$(CH_3)_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.0 (s), 155.3 (d), 141.6 (s), 136.2 (d), 130.7 (d), 127.4 (d), 116.1 (t), 38.9 (s), 27.1 (q), 26.6 (2q), 20.9 (q), 18.6 (q) ppm. GC/MS (EI): 178 (M+, 7), 163 (19), 145 (8), 135 (35), 121 (19), 107 (35), 93 (60), 77 (26), 65 (10), 55 (14), 43 (100). IR (neat, ν/cm-1): 2965, 1677, 1621, 1451, 1359, 1256, 970.

General procedure B for 2-cyclopentenylketone synthesis:

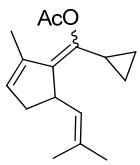
Cyclopropyl-[2-methyl-5-(2-methyl-propenyl)-cyclopent-1-enyl]-methanone (19a)



19a Methylene chloride (10 mL) was added to a mixture of gold complex [AuCl(PPh_3)] (49.4 mg, 0.10 mmol) and $AgSbF_6$ (34.3 mg, 0.10 mmol), and the reaction mixture was stirred for 10 min under argon atmosphere. The resulting solution was filtered through a pad of celite. A solution of **15a** (2.46 g, 10 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was stirred for 5 min. Methanol (10 mL) and K_2CO_3 (2.76 g, 20 mmol) were added to the reaction mixture. The resulting mixture was stirred for 4 hours and concentrated. The residue was neutralized with 1N HCl and extracted 3 times with MTBE (30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography on silica gel, eluent: hexane:MTBE (10:1) to yield **19a** (1.59 g, 78%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.09 (d, *J* = 9.8 Hz, 1H), 4.03-3.90 (m, 1H), 2.57-2.28 (m, 2H), 2.19-2.08 (m, 1H), 2.03 (s, 3H, CH_3), 2.01-1.95 (m, 1H), 1.69 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.56-1.44 (m, 1H), 1.11-1.04 (m, 1H), 1.00-0.94 (m, 1H), 0.82-0.76 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.1 (s), 151.4 (s), 140.1 (s), 130.9 (s), 128.4 (d), 45.7 (d), 38.9 (t), 30.5 (t), 25.7 (q), 20.1 (d), 17.9 (q), 16.6 (q), 11.2 (t), 10.6 (t) ppm. GC/MS (EI): 204 (M+, 39), 189 (100), 161 (67), 147 (51), 133 (74), 119 (28), 105 (44), 91 (56), 77 (30), 69 (96), 55 (26), 41 (67). IR (neat, ν/cm-1): 2915, 1663, 1614, 1444, 1384, 1196, 1172, 1113, 972, 848. HRMS (EI): m/z: calcd. for $C_{14}H_{20}O$ 204.1514; found: 204.1516.

In another example, the reaction mixture was concentrated prior methanolysis and the crude product was purified by column chromatography on silica gel, eluent: hexane:MTBE (10:1). Compound **18a** was obtained as a colorless oil (2.45 g, 99% yield).

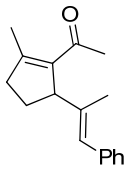
Cyclopropyl(2-methyl-5-(2-methylprop-1-enyl)cyclopent-2-enylidene)methyl acetate (18a)



18a 2 Isomers in a ratio of 4:1. ^{1}H-NMR (300 MHz, $CDCl_3$): *δ* = 5.71, 5.58 (2 bs, 1H), 5.22, 5.05 (2d, *J* = 9.5 Hz, 1H), 3.85-3.80, 3.65-3.59 (2m, 1H), 2.83-2.59 (m, 1H), 2.10 (s, 3H), 2.10-1.62 (m, 5H), 1.66 (s, 3H), 1.63 (s, 3H), 0.74-0.48 (m, 4H) ppm. ^{13}C-NMR (75 MHz,

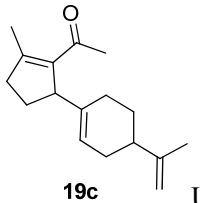
$CDCl_3$), major isomer: δ = 169.3 (s), 140.8 (s), 138.7 (s), 137.1 (s), 135.0 (d), 128.9 (d), 128.6 (s), 41.0 (d), 38.3 (t), 25.5 (q), 20.3 (q), 17.8 (q), 17.2 (q), 12.1 (d), 7.2 (t), 5.6 (t) ppm. GC/MS (EI): 246 (M+, 25), 200 (64), 189 (4), 161 (5), 148 (76), 133 (45), 119 (9), 105 (15), 91 (21), 79 (12), 69 (100), 55 (7), 41 (29). IR (neat, ν/cm-1): 2969, 2925, 1753, 1446, 1369, 1202, 1172, 1044. HRMS (EI): m/z: calcd. for $C_{16}H_{22}O_2$ 246.1620; found: 246.1625.

1-[2-Methyl-5-(1-methyl-2-phenyl-vinyl)-cyclopent-1-enyl]-ethanone (19b)



19b Using general procedure B, a mixture of **15c** (2.82 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **19c** as a yellow oil (1.92 g, 88 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.14 (m, 5H, Ar-H), 6.28 (s, 1H), 3.85-3.75 (m, 1H), 2.64-2.53 (m, 1H), 2.48-2.37 (m, 1H), 2.28-2.21 (m, 1H), 2.20 (s, 3H, CH3), 2.12 (s, 3H, CH3), 1.81 (s, 3H, CH3), 1.78-1.69 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.2 (s), 155.3 (s), 141.0 (s), 138.2 (s), 137.7 (s), 128.8 (d), 128.1 (d), 126.1 (d), 125.1 (d), 56.7 (d), 39.3 (t), 29.9 (q), 28.9 (t), 16.7 (q), 15.9 (q) ppm. GC/MS (EI): 240 (M+, 51), 225 (19), 197 (18), 181 (10), 165 (15), 149 (100), 141 (11), 128 (12), 115 (24), 105 (11), 91 (31), 77 (11), 43 (57). IR (neat, ν/cm-1): 2937, 1709, 1493, 1450, 1359, 1206, 751, 701. HRMS (EI): m/z: calcd. for $C_{17}H_{20}O$ 240.1514; found: 240.1517.

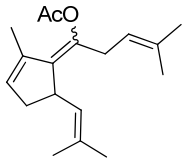
1-[5-(4-Isopropenyl-cyclohex-1-enyl)-2-methyl-cyclopent-1-enyl]-ethanone (19c)



19c Using general procedure B, a mixture of **15c** (2.86 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **19d** as a yellow oil (2.12 g, 87 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.45-5.38 (m, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 3.62-3.50 (m, 1H), 2.58-2.43 (m, 1H), 2.33 (ddd, J = 17.8, 9.0, 4.5 Hz, 1H), 2.15 (s, 3H, CH_3), 2.20-2.02 (m, 3H), 2.07 (s, 3H, CH_3), 2.01-1.86 (m, 3H), 1.85-1.77 (m, 1H), 1.72 (s, 3H, CH_3), 1.62 (ddd, J = 17.9, 9.0, 4.5 Hz, 1H), 1.50-1.38 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5 (s), 154.5 (s), 149.7 (s), 139.8 (s), 137.6 (s), 120.7 (d), 108.5 (t), 54.2 (d), 41.1 (d), 39.3 (t), 30.6 (t), 29.8 (q), 29.1 (t), 27.8 (t), 26.8 (t), 20.8 (q), 16.6 (q) ppm. GC/MS (EI): 244 (M+, 59), 229 (8), 201 (35), 181 (10), 175 (23), 161 (32), 147 (18), 133 (54), 121 (56), 105 (25), 91 (32), 79 (28), 67

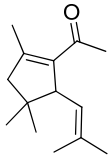
(9), 53 (12), 43 (100).IR (neat, ν/cm-1): 2933, 1675, 1434, 1357, 889. HRMS (EI): m/z: calcd. for $C_{17}H_{24}O$ 244.1827; found: 244.1834.

4-Methyl-1-(2-methyl-5-(2-methylprop-1-enyl)cyclopent-2-enylidene)pent-3-enyl acetate (18d)



18d 2 Isomers in a ratio of 4:1. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.75, 5.56 (2 bs, 1H), 5.25-4.98 (m, 2H), 3.91-3.82, 3.75-3.60 (2m, 1H), 3.32-2.82 (m, 1H), 2.80-2.43 (m, 1H), 2.10 (s, 3H), 2.10-1,62 (m, 2H), 1.99 (s, 3H), 1.86 (s, 3H), 1.75-1.55 (m, 9H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.7, 169.5 (s), 141.0, 139.6 (s), 137.5 (s), 136.3, 136.2 (s), 135.6, 133.8 (d), 133.4, 133.0 (s), 129.0, 128.9 (d), 129.0, 128.6 (s), 120.6, 119.9 (d), 40.6, 39.5 (d), 38.6, 38.0 (t), 30.4, 29.7 (t), 25.7, 25.6 (q), 25.5 (q), 20.8, 20.6 (q), 17.9, 17.8 (q), 17.7, 17.6 (q), 17.1, 16.3 (q) ppm. GC/MS (EI): 274 (M+, 7), 232 (64), 218 (20), 177 (22), 163 (20), 147 (18), 119 (16), 107 (100), 91 (21), 79 (17), 69 (25), 55 (7), 41 (20). IR (neat, ν/cm-1): 2970, 2925, 1753, 1446, 1368, 1213, 1069. HRMS (EI): m/z: calcd. for $C_{18}H_{26}O_2$ 274.1933; found: 274.1931.

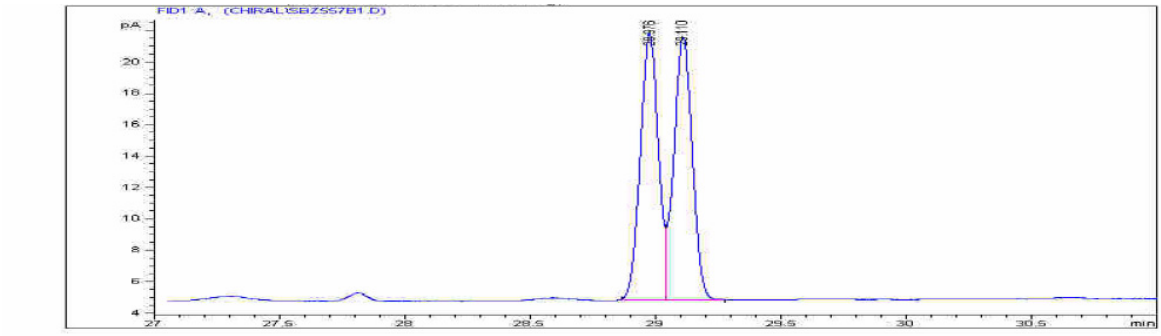
***rac*-1-[2,4,4-Trimethyl-5-(2-methyl-propenyl)-cyclopent-1-enyl]-ethanone (19e)**



19e Using general procedure B, a mixture of **15e** (2.48 g, 10 mmol) and gold complex $Au(PPh_3)SbF_6$ (0.10 mmol) were reacted and methanolyzed to give **19e** as a colorless liquid (1.13 g, 55 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.94 (d, *J* = 10.7 Hz, 1H), 3.33 (d, *J* = 10.7 Hz, 1H), 2.37 (d, *J* = 17.6 Hz, 1H), 2.15 (d, *J* = 17.6 Hz, 1H), 2.11 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.89 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5 (s), 152.4 (s), 138.7 (s), 132.6 (s), 125.1 (d), 55.9 (d), 53.8 (t), 41.0 (s), 29.9 (q), 29.7 (q), 25.8 (q), 24.6 (q), 17.9 (q), 17.0 (q) ppm. GC/MS (EI): 206 (M+, 25), 191 (100), 173 (75), 161 (27), 149 (27), 135 (42), 121 (34), 107 (33), 91 (42), 77 (23), 55 (15), 43 (100). IR (neat, ν/cm-1): 2957, 2915, 1677, 1610, 1429, 1355, 1240. HRMS (EI): m/z: calcd. for $C_{14}H_{22}O$ 206.1671; found: 206.1665.

(5*S*)-1-[2,4,4-Trimethyl-5-(2-methyl-propenyl)-cyclopent-1-enyl]-ethanone ((5*R*)-19e). This compound was prepared from (1*S*,3*S*)-**15e** in an analogous way. 89% ee. $[\alpha]^{22}$ = +169.2 (*c* = 1.15, $CHCl_3$).

GC chromatogram of *rac*-**19e**



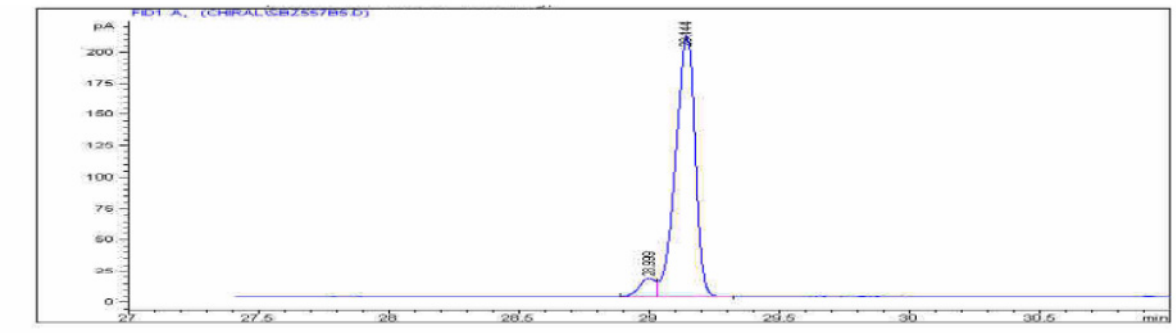
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	28.976	BV	0.0786	84.73908	16.88049	49.82680
2	29.110	VB	0.0777	85.32818	16.68453	50.17320
Totals :				170.06726	33.56502	

GC chromatogram of *(R)*-**19e**



Area Percent Report

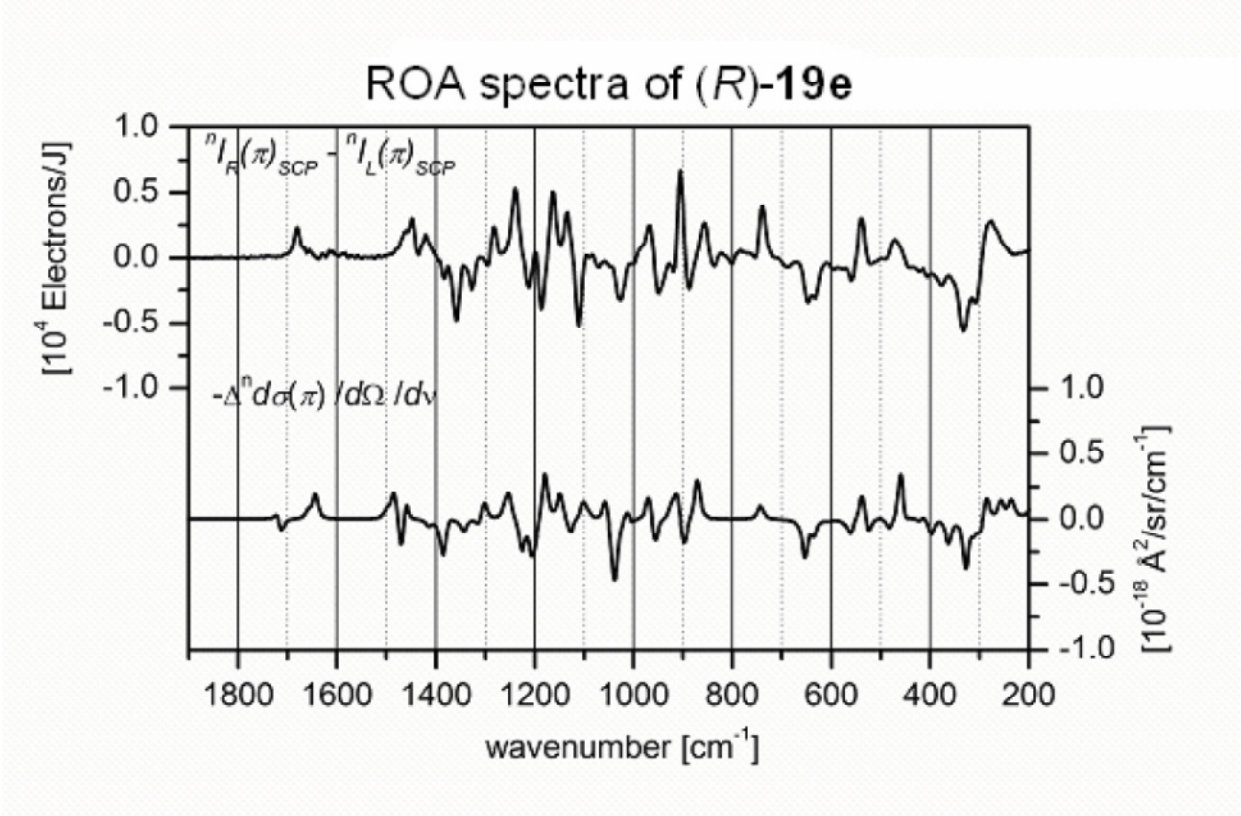
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	28.999	BV	0.0658	60.20705	14.11743	5.28674
2	29.144	VB	0.0845	1078.62390	207.90990	94.71326
Totals :				1138.83096	222.02733	

The absolute configuration of (*R*)-**19e** was determined by comparing the vibrations of a measured ROA (Raman Optical Activity) spectra (below) with those of the theoretical spectra, calculated at

the B97-1/pc-2 level with the Gaussian program (above).[1a,b,d] ROA calculations at the TDHF/DPS level was carried out with the Dalton program.[1c]



[1] Wessjohann, L. A.; Fulhorst, M.; Zakharova, S. *Pol. J. Chem.* **2006**, *80*, 673-678.

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[7] Armesto, D.; Gallego, M. G.; Horspool, W. M.; Agarrabeitia, A. R. *Tetrahedron* **1995**, *51*, 9223-9240.

Chapter 3

Mechanistic Insights in Gold-Stabilized Nonclassical Carbocations: Gold-Catalyzed Rearrangement of 3-Cyclopropyl Propargyl Acetates

CHAPTER 3

Mechanistic Insights in Gold-Stabilized Nonclassical Carbocations: Gold-Catalyzed Rearrangement of 3-Cyclopropyl Propargyl Acetates

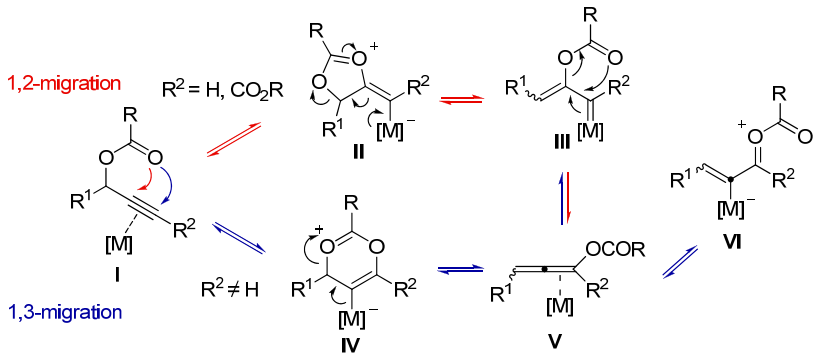
D. Garayalde, E. Gómez-Bengoa, X. Huang, A. Goeke and C. Nevado*

(*J. Am. Chem. Soc.* **2010**, *132*, 4720-4730)

3.1 Introduction

From the seminal discovery of the Zn-mediated rearrangement of propargyl acetates reported by Ohloff et al. in 1976, the chemistry of propargyl esters has experienced an exponential growth.[1] Ten years later, a related Pd-catalyzed cyclization of 1-ethynyl-2-propenyl acetates to give 2-cyclopentenones was reported by Rautenstrauch and co-workers.[2] Although lacking an in depth mechanistic study, the formation of a Pd-carbene intermediate was already postulated. Work from Ohe and Uemura with ruthenium,[3] and Malacria with platinum[4] re-opened the interest in this class of transformations at the beginning of this decade. Later, Toste demonstrated that intermediate achiral carbenes are an insufficient explanation for the observed chirality transfer in a gold promoted version of the Rautenstrauch reaction.[5] Now, after 30 years of research mainly driven by the irrumption of platinum and gold complexes in modern catalysis, a more clear mechanistic picture has been evolved for these transformations (Scheme 1).[6]

Scheme 1. 1,2- vs. 1,3-Carboxylate Migration

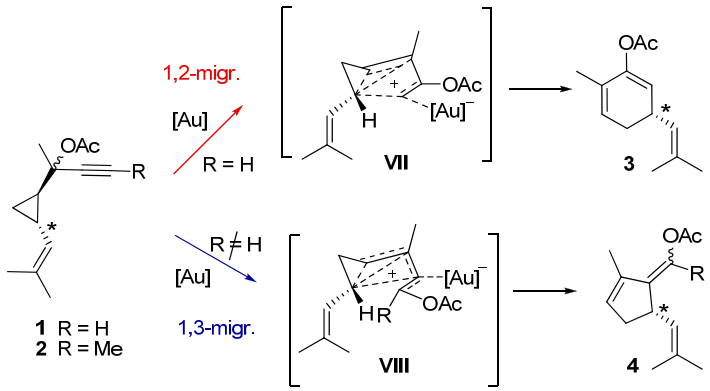


Gold in particular has proven to efficiently activate propargyl carboxylates (**I**) towards 1,2-acyloxy migration and/or [3,3]-sigmatropic acyloxy rearrangement at room temperature (red and blue paths respectively).[7] These two competitive processes seem to be mechanistically related: 1,2-migration proceeds via metal carbene (**III**), whereas [3,3]-sigmatropic rearrangement proceeds via allenyl acetate (**V**) in a single process or stepwise by a second acetate migration from **III** (Scheme 1).[8] Allenyl acetates **V** can be further activated in the presence of the metal catalyst to give **VI**, triggering an extensive palette of transformations. It is widely accepted that terminal or electron poor alkynes react via 1,2-[9,10] whereas internal alkynes prefer the 1,3-migration pathway[11] and only few exceptions to this general pattern have been described.[12]

We have recently reported a new Au-catalyzed homo-Rautenstrauch rearrangement of 1-cyclopropyl propargylic esters (**1**, **2**) to give 5-, 6- and also 7-membered ring vinyl acetates under

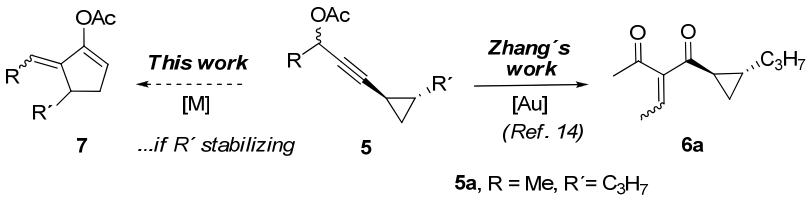
mild conditions (Scheme 2).[13] A key factor in the successful development of this transformation is the presence of a substituent at the cyclopropyl ring able to stabilize the positive electron density developed during the concomitant ring opening process. The almost complete chirality transfer we observed in these reactions suggested that gold-stabilized nonclassical carbocations with a certain configurational stability (**VII**, **VIII**) might be involved, since enantiomerically enriched cyclohexadienyl (**3**) and cyclopentenyl acetates (**4**) could be obtained when optically active starting materials were employed.

Scheme 2. Au-Catalyzed Homo-Rautenstrauch Rearrangement of 1-Cyclopropyl Propargylic Acetates



To get a further insight in the reactive species involved in these transformations, we decided to explore the chemistry of related 3-cyclopropyl propargylic carboxylates **5** (Scheme 3). Such settings had already been studied by Zhang and co-workers.[14] In the presence of gold catalysts, Zhang´s group developed an elegant method to obtain *α*-ylidene-*β*-diketones as a result of the 1,3-migration of the acyl group onto the alkyne moiety followed by acetate fission. The cyclopropyl ring behaved in this case as mere spectator in the reaction (**5a** to **6a**, Scheme 3). Based on our previous experience, we decided to explore whether the presence of a group able to stabilize a developing positive electron density could induce the cyclopropyl ring opening to give cyclopentannulation products **7** instead.

Scheme 3. Au-Catalyzed Acetate Migration+Fission to *α*-Ylidene-*β*-diketones vs. Cyclopentannulation



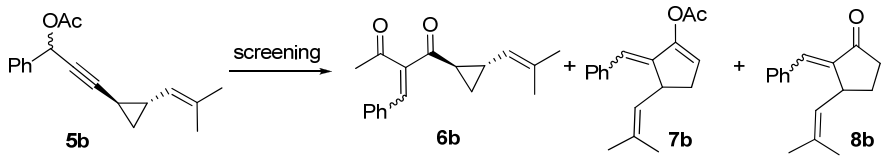
Herein, we report our in depth investigation on the cyclization of 3-cyclopropyl propargylic carboxylates and related species. We also present a DFT computational study on the reaction mechanism, which reveals the decisive intermediates determining the stereoselectivity of these transformations. This work also sheds light on the role of the substituents at the propargylic position in defining the reaction pathway since products of both, 1,2- and 1,3-acyloxy migration pathways, have been found in these processes.

3.2 Results and discussion

3.2.1 Reaction Optimization.

3-((2-Methylpropenyl)cyclopropyl propargyl)-1-phenylprop-2-ynyl acetate (**5b**) was used as benchmark substrate to find suitable reaction conditions. The results of this optimization are summarized in Table 1. In the presence of $PtCl_2$ in toluene as solvent, no reaction was observed at room temperature (Table 1, entry 1). Heating to 80 ºC, **5b** was completely consumed affording a complex mixture of products from which α-ylidene-*β*-diketone **6b** could be isolated albeit in low yield (Table 1, entry 2). This result reflects the preference for the acetate fission pathway vs. the cyclopropyl ring opening with Pt salts. We then decided to turn our attention towards gold catalysts in CH_2Cl_2 as a solvent. Treatment with gold(I) chloride delivered a complex mixture due to partial decomposition of the starting material even at room temperature (Table 1, entry 3). Cationic complexes generated by chloride abstraction from $[(Ph_3P)Au(Cl)]$ such as $[(Ph_3P)Au(NTf_2)]$ and $[(Ph_3P)Au(SbF_6)]$ provided, for the first time, cyclopentene acetate **7b** as the major produt of the reaction (Table 1, entries 4 and 5). Surprisingly, dichloro(pyridine-2-carboxylato)gold(III), the catalyst of choice in Zhang´s transformations,[14] did not produce the expected *α*-ylidene-*β*-diketone **6b**, but only **7b** in moderate yield upon heating to 50 ºC (Table 1, entry 6). The use of a bulky phosphine ligand as in $\{[(t\text{Bu})_2(\text{BPH})]PAu(SbF_6)\}$ afforded **7b** in 85% yield as a 2:1 (*E*:*Z*) mixture of isomers. (Table 1, entry 7) Finally, $[(IPr)Au(NTf_2)]$ afforded the desired alkylidene cyclopentenyl acetate **7b** in almost quantitative yield after 5 minutes of reaction (Table 1, entry 8). In situ methanolysis of the product produced cyclopentenone **8b** in 75% yield (Table 1, entry 9). Notably, in all the cases studied, **7b** was obtained as a variable *E:Z* mixture of isomers.[15]

Table 1. Optimizing Reaction Conditions for the Cyclization of 3-Cyclopropyl Propargyl Acetate **5b**



Entry	Catalyst (mol %)	Conditions	Time (h)	Conversion (%)[a]	Yield (%)[b] (ratio **6b**:**7b**)
1	$PtCl_2$ (5)	Toluene, 25 ºC	15	0	-
2	$PtCl_2$ (5)	Toluene, 80 ºC	12	100	<10 (100:0)
3	AuCl (2)	CH_2Cl_2, 25 ºC	0.5	90	Complex Mixture
4	$[(Ph_3P)Au(NTf_2)]$ (3)	CH_2Cl_2, 25 ºC	0.25	100	75 (1:8)
5	$[(Ph_3P)Au(SbF_6)]$ (3)	CH_2Cl_2, 25 ºC	0.25	100	85 (1:10)
6	$LAuCl_2$[c] (5)	CH_2Cl_2, 50 ºC	1	100	65 (1:>99)
7	$\{[(t\text{Bu})_2(\text{BPH})]P Au(SbF_6)\}$[d] (5)	CH_2Cl_2, r.t.	0.1	100	85[e]

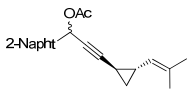
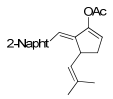
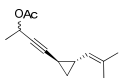
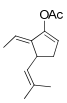
8	[(IPr)Au(NTf_2)] (5)	CH_2Cl_2, r.t.	0.1	100	90 (1:>99)[f]
9	[(IPr)Au(NTf_2)] (5)	i. CH_2Cl_2, 25 ºC ii.K_2CO_3 (2equiv.), MeOH	0.1	100	75 (**8b**)[f]

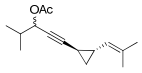
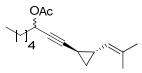
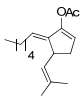
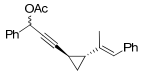
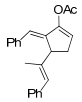
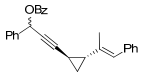
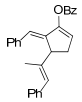
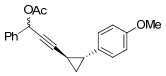
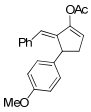
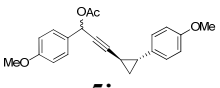
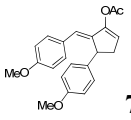
[a] Conversion calculated by ^{1}H-NMR. [b] Isolated yield after column chromatography.[c] L = Pyridine-2-carboxylate.[d] BPH: biphenyl [e] Compound **7b** was obtained as a 2: 1 (*E:Z*) mixture. [f] Compounds **7b** and **8b** were obtained as a 15: 1 (*E:Z*) mixture.

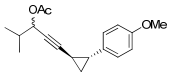
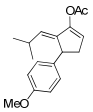
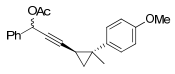
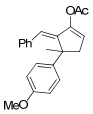
3.2.2 General Reactivity.

Once the reaction conditions for the selective cyclization of 3-cyclopropyl propargyl carboxylate **5b** had been established, we decided to explore the scope of this transformation. First, we focused on substrates containing secondary acetates, which proved to be unsuccessful in our previously developed homo-Rautenstrauch rearrangement reaction.[13a] These results have been summarized in Table 2. To our delight, 2-naphthyl derivative **5c** afforded vinyl acetate **7c** in 84% yield under the optimized reaction conditions (Table 2, entry 1). The presence of alkyl substituents at the propargylic position was also examined. Thus, substrates **5d-f** were efficiently transformed into the corresponding cyclopentenyl acetates (**7d-f**) (Table 2, entries 2-5). The cyclopropyl ring cleavage can be also stabilized by a 1-phenylprop-1-en-2-yl moiety as in **5g** (Table 2, entries 6, 7) and different migrating groups such as benzoates (**5h**) were tolerated (Table 2, entries 8, 9). In some cases, the dichloro(pyridine-2-carboxylato)gold(III) catalyst seemed to give better results in terms of yield and/or *E:Z* selectivity at the exocyclic olefin compared to [(IPr)Au(NTf_2)] (Table 2, entries 4, 6, 8, 10, 12, 14, 16 vs. 5, 7, 9, 11, 13, 15, 17). Remarkably, except for **5j**, both catalysts delivered clean and complete conversions and no α-ylidene-β-diketones (**6**) were observed. As it was mentioned above, *E* isomers were always obtained as major products of these reactions.[15] Attempts to transform *Z* into thermodynamically favored *E* isomers in the presence of gold catalysts failed.[16] The determining step for the *E* vs. *Z* exocyclic alkene formation seems to be thus, under kinetic control.

Table 2. Au-Catalyzed Cyclization of 3-Cyclopropyl-Propargyl-Carboxylates

Entry	Substrate	Conditions[a]	Product[b]	Yield (%)[c,d] (*E*:*Z* ratio)[e]
1	 **5c**	A	 **7c**	84 (14:1)
2	 **5d**	A	 **7d**	75 (10 : 1)

3	 **5e**	A	 **7e**	77 (7:1)
4	 **5f**	A	 **7f**	65 (50:1)
5	**5f**	B	**7f**	96 (17:1)
6	 **5g**	A	 **7g**	73 (5:1)
7	**5g**	B	**7g**	84 (10:1)
8	 **5h**	A	 **7h**	51 (14:1)
9	**5h**	B	**7h**	87 (14:1)
10	 **5i**	A	 **7i**	80 (3 : 1)
11	**5i**	B	**7i**	82 (3.4:1)
12	 **5j**	A	 **7j**	_ [f]
13	**5j**	B	**7j**	75 (100:0)

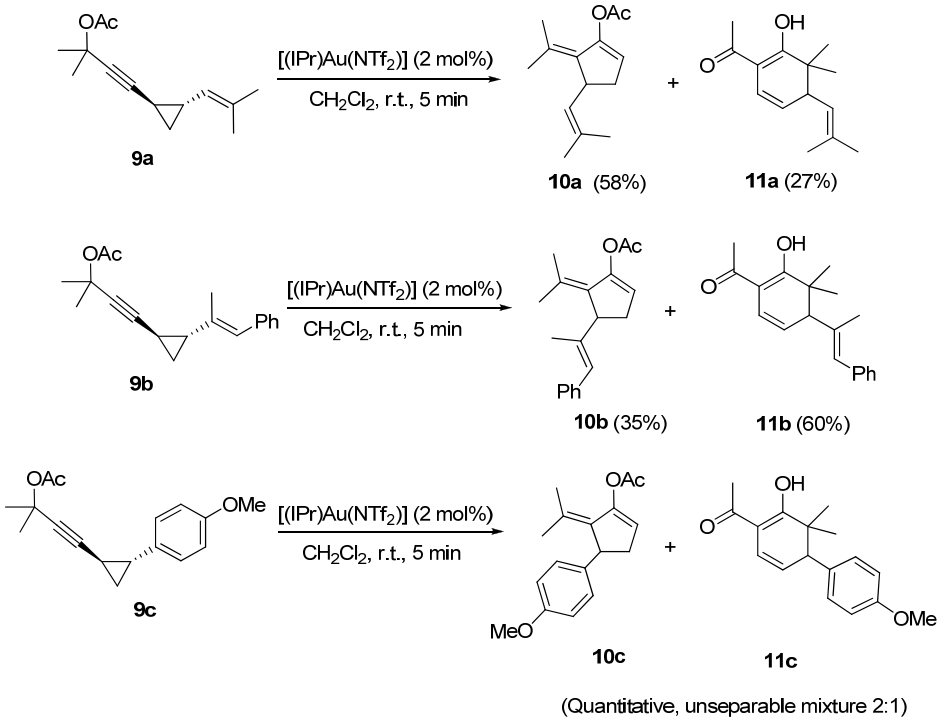
14	 **5k**	A	 **7k**	84 (5:1)
15	**5k**	B	**7k**	94 (100:0)
16	 **5l**	A	 **7l**	84 (3:1)
17	**5l**	B	**7l**	86 (50:1)

[a] Reaction Conditions A: [(IPr)Au(NTf_2)] (5 mol%), CH_2Cl_2, 25 ºC, 30 min.; B: dichloro(pyridine-2-carboxylato)gold (III) (5 mol%), CH_2Cl_2, 50 ºC, 30 min. [b] Only the major product is shown. [c] Isolated yield after column chromatography. [d] Determined by ^{1}H-NMR in the reaction mixture. [e] The yields after methanolysis of the reaction mixtures to give the corresponding ketones can be found in the supporting information. [f] Decomposition was observed.

3.2.3 Cyclization of Tertiary Acetates.

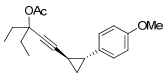
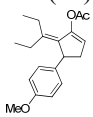
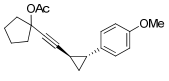
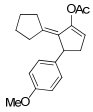
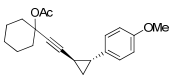
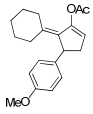
We focused next on the reaction of tertiary propargyl acetates, which have unraveled interesting mechanistic features of these transformations. When substrate **9a** was treated with [(IPr)Au(NTf_2)] (5 mol%) in CH_2Cl_2 at room temperature, the expected product **10a** was obtained in 58% yield. A careful analysis of the reaction mixture revealed the formation of 1,3-diketone **11a** isolated in 27% yield in its enolic form (Scheme 4). A similar behavior in the presence of [(IPr)Au(NTf_2)] as catalyst was observed for substrates **9b** and **9c** affording cyclopentenyl acetates **10b-c** and diketones **11b-c** in 1:2 and 2:1 ratio respectively. *In our view, formation of **11a-c** can be explained by a 1,2-acetoxy migration pathway followed by cyclopropyl ring opening and cyclization terminating with the fission of the acetate group.* Formation of products from both 1,2- and 1,3-acyloxy migration pathways from the same substrate under a certain set of conditions is rare and deserves further attention. Computational studies on these systems have been performed and the results will be discussed in following section.

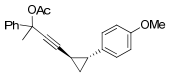
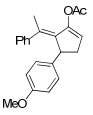
Scheme 4. Reaction of Tertiary Acetates with [(IPr)Au(NTf_2)]



After extensive experimentation, we found that treatment of **9a** with [$(PhO)_3PAu(SbF_6)$] (5 mol%) allowed the clean formation of cyclopentenyl acetate **10a** in 81% yield (Table 3, entry 1). Similarly, **10b-d** were efficiently produced under the same reaction conditions (Table 3, entries 2-4). The reaction of cyclopentyl and cyclohexyl substituted derivatives **9e-f** proceeded cleanly at -20 ºC to give products **10e-f** in 85% yield (Table 3, entries 5 and 6). Finally, compound **9g** was cyclized to give **10g** as a 4:1 mixture of isomers (Table 3, entry 7).[15]

Table 3. Au-Catalyzed Cyclization of 3-Cyclopropyl Propargyl Tertiary Carboxylates

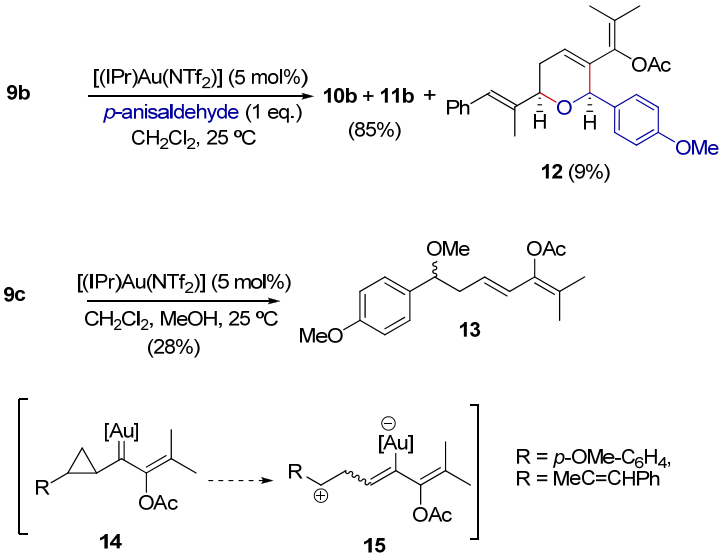
Entry	Substrate	Reaction Conditions[a]	Product[b] (Yield, %)
1	**9a**	[$(PhO)_3PAu(SbF_6)$], T^a = 25 ºC, 30 min	**10a** (81)
2	**9b**	[$(PhO)_3PAu(SbF_6)$] , T^a = 25 ºC, 30 min	**10b** (90)
3	**9c**	[$(PhO)_3PAu(SbF_6)$], T^a = 25 ºC, 1 h	**10c** (78)
4	 **9d**	[$(PhO)_3PAu(SbF_6)$], T^a = 25 ºC, 1 h	 **10d** (71)
5	 **9e**	[$(PhO)_3PAu(SbF_6)$], T^a = - 20 ºC, 1 h	 **10e** (85)
6	 **9f**	[$(PhO)_3PAu(SbF_6)$] , T^a = - 20 ºC, 1 h	 **10f** (85)

7	 **9g**	$[(PhO)_3PAu(SbF_6)]$, T^a = 25 ºC, 1 h	 **10g** (78)[c]

[a] Reactions run in CH_2Cl_2 as solvent with 5 mol% catalyst. [b] Isolated yield after column chromatography. [c] Obtained as a 4:1 (*E*:*Z*) mixture of isomers.

To further confirm the 1,2-acetoxy migration pathway operating in the reaction of tertiary acetates with $[(IPr)Au(NTf_2)]$ as catalyst, the following experiments were designed (Scheme 5). Reaction of **9b** in the presence of one equivalent of *p*-anisaldehyde gave a mixture of **10b**+**11b** in 85% yield together with dihydropyran **12** in 9% yield. The latter can be explained by a [4C+2C] cycloaddition reaction between 1,4-dipole **15** (generated in situ along the 1,2-migration path) and *p*-anisaldehyde as dipolarophile.[17] On the other hand, when **9c** was treated with $[(IPr)Au(NTf_2)]$ in MeOH as a co-solvent compound **13** was isolated in 28% yield. Formation of both, **12** and **13** is a clear indication of a 1,2-acyloxy migration manifold via intermediates **14** and **15** operating in competition with the predicted [3,3]-acyloxy rearrangement.

Scheme 5. Evidence for the 1,2-Acyloxy Migration Pathway in the Reaction of Tertiary Acetates with $[(IPr)Au(NTf_2)]$ as Catalyst

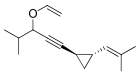
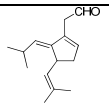
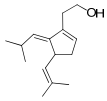
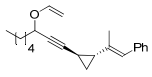
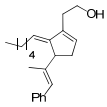
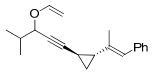
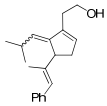


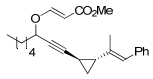
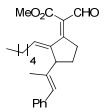
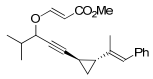
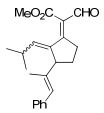
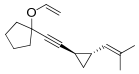
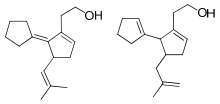
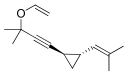
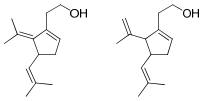
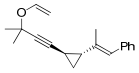
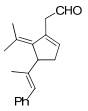
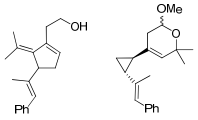
The results summarized in Schemes 4 and 5 and Table 3 can be explained in light of the distinct nature of the reaction intermediates depending on the ligand bound to the gold center.[18] $[(PhO)_3PAu(SbF_6)]$ displays a more electrophilic character compared to $[(IPr)Au(NTf_2)]$ due to the π-acceptor phosphite ligand. The decrease in the gold-to-C π-donation might enhance the carbocationic character of the reaction intermediates, thus favoring the cyclopentannulations products (**10**). In contrast, the IPr (1,3-bis(2,6-disiopropylphenyl)imidazol-2-ylidene) ligand is strongly σ-donating and only weakly π-acidic, thus increasing the carbene-like reactivity favoring intermediate **14** (also preferred by steric reasons) over the allene intermediate and thus triggering the formation products such as **11**, **12** or **13**.

3.2.4 Cyclization of Propargyl Vinyl Ethers.

In addition to carboxylic groups (acetates, benzoates, etc…), propargyl vinyl ethers are also suitable motifs for rearrangement across the triple bond upon metal activation.[19] We expected to form two new C-C bonds by coupling the [3,3]-sigmatropic rearrangement to the cyclopropyl ring opening reaction. Thus, substrate **16a** was treated with [(IPr)Au(NTf_2)] (5 mol%) delivering the corresponding cyclopent-1-enyl aldehyde **17a** in 71% yield.[15] To achieve higher yields, the Au-catalyzed cyclization was coupled to an in situ reduction of the aldehyde with $NaBH_4$ as previoustly reported by Toste and co-workers (Table 4, entry 2).[19b] A similar protocol was applied for substrates **16b-c** which gave the corresponding alcohols **18b-c** in excellent yields (Table 4, entries 3 and 4). Interestingly, electron-deficient vinyl ethers such as **16d** and **16e** were cleanly transformed into the corresponding (*Z*)-methyl-2-(2-methylenecyclopentylidene)-3-oxopropanoates **17d** and **17e** under the abovementioned reaction conditions (Table 4, entries 5 and 6).[15] It is important to note that no heterocyclization on the allenyl carbonyl intermediate to give 3-cyclopropyl substituted furans was observed, as previously reported by Kirsch and co-workers for similar settings.[20] In contrast to the mechanistic dichotomy manifold observed in the migration of tertiary acetates with [(IPr)Au(NTf_2)], the rearrangement of tertiary vinyl ethers under similar reaction conditions delivered only the products derived of a propargyl-Claisen rearrangement. Substrates **16f** and **16g** with a 2-methyl-2-propen-1-yl substituent at the cyclopropyl ring delivered upon $NaBH_4$ reduction the expected alcohols **18f** and **18g** together with **18f´** and **18g´** (Table 4, entries 7 and 8).[21] The reaction of **16h** afforded aldehyde **17h** in modest yield (Table 4, entry 9), whereas the reductive work-up in MeOH allowed us to isolate alcohol **18h** in 70% yield and a small amount of **19**. The latter is presumably formed by trapping the carbocationic intermediate formed during [3,3]-rearrangement in the first step of the reaction with MeOH, which is used as solvent in the subsequent step (Table 4, entry 10).[19b]

Table 4. Au-Catalyzed Cyclization of 3-Cyclopropyl Propargyl Enol Ethers

Entry	Substrate	Conditions[a]	Product(s), (Yield, %),[b,c] (*E*:*Z* ratio)[d]
1	 **16a**	A	 **17a** (71), (2:1)
2	**16a**	B	 **18a** (97), (2:1)
3	 **16b**	B	 **18b** (88), (3:1)
4		B	

	16c		**18c** (88), (1:1)
5	 **16d**	A	 **17d** (97), (5:1)
6	 **16e**	A	 **17e** (82), (1:1)
7	 **16f**	B [e]	 **18f** + **18f´** (90, 17:1 ratio)
8	 **16g**	B [e]	 **18g** + **18g´** (75, 5:1 ratio)
9	 **16h**	A [e]	 **17h** (58)
10	**16h**	B [e]	 **18h** (70) **19** (10)

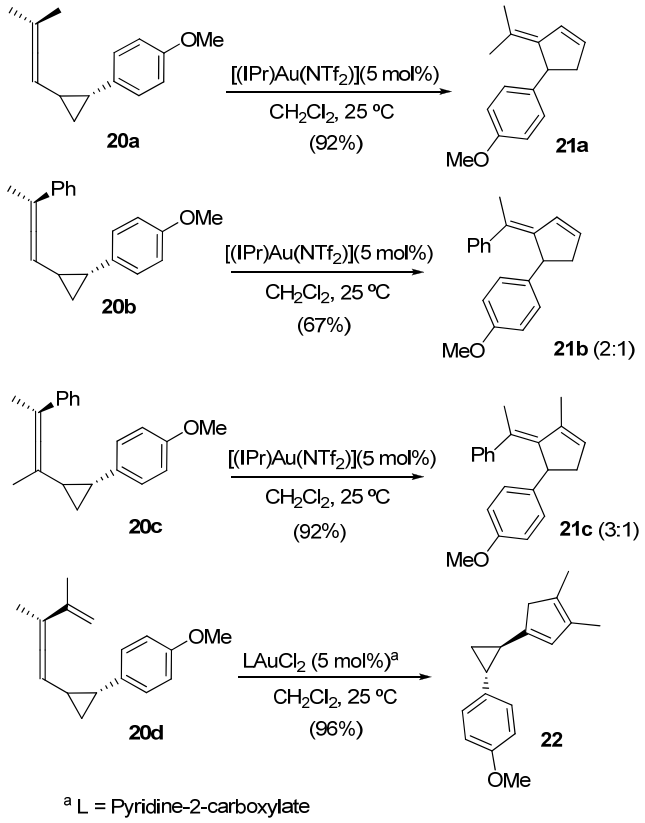
[a] Reaction Conditions A: [(IPr)Au(NTf_2)] (5 mol%), CH_2Cl_2, 25 ºC, 30 min.; B: i. [(IPr)Au(NTf_2)] (5 mol%), CH_2Cl_2, 25 ºC, 30 min. ii. $NaBH_4$ (5 equiv.), MeOH. [b] Only the major product is shown. [c] Isolated yield after column chromatography. [d] Determined by ^{1}H-NMR in the reaction mixture. [e] Reaction time: 90 min.

3.2.5 Cyclization of Non-Activated Allenes.

The cyclization of propargylic esters and enol ethers presented above presumably proceed by the formation of an oxo-allene intermediate (see **V** in Scheme 1) upon Au-catalyzed [3,3]-sigmatropic rearrangement. To further confirm this hypothesis, we decided to explore the reactivity of "non-activated" cyclopropyl allenes in the presence of gold complexes. We were pleased to observe that substrate **20a** reacted in the presence of 5 mol% of [(IPr)Au(NTf_2)] to

afford 2-(ethylylidene)cyclopent-3-enyl **21a** in excellent yield following the previously proposed sequence: gold activation of the allene-cyclopropyl ring opening-cyclization (Scheme 6). Tri- and tetrasubstituted allenes were well tolerated as shown by the reactions of **20b** and **20c** to give cyclopentenes **21b** and **21c** in 67 and 92% yield, respectively. When a 1-methyleth-2-enyl substituent is placed at the terminal position of the allene (**20d**), the reaction in the presence of [(IPr)Au(NTf_2)] afforded a complex reaction mixture. In the presence of dichloro(pyridine-2-carboxylato)gold(III), a clean 6-π-electrocyclization takes place to give bicyclic compound **22** in almost quantitative yield as previously reported by other groups.[22]

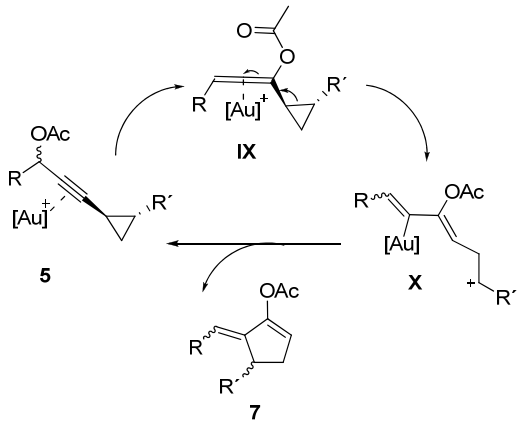
Scheme 6. Cyclization of 3-Cyclopropyl Allenes



3.3 Mechanistic Discussion

A simplified vision of the cyclization of 3-cyclopropyl propargylic acetates **5** presumably involves an allenyl intermediates **IX**, which undergoes ring expansion to form a 1,5-dipole **X** where the carbocation is stabilized by aromatic or vinylic groups. From **X**, a cyclization to form alkylidene cyclopentenyl acetates **7** can be proposed (Scheme 7).

Scheme 7. Simplified Mechanism for the Cyclopentannulation Reaction of 3-Cyclopropyl Propargyl Acetates

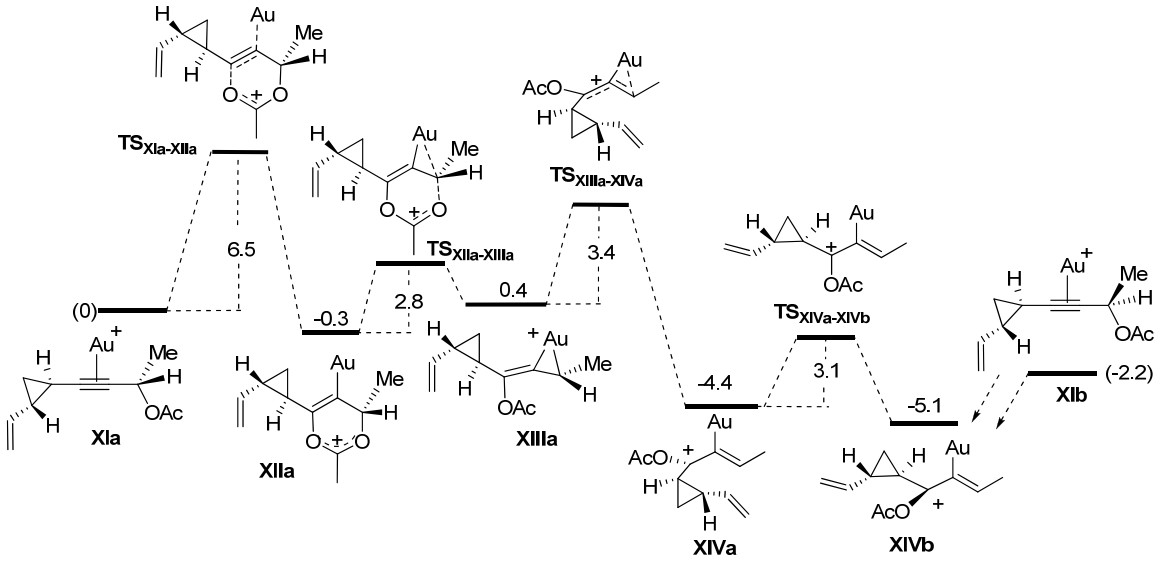


To gain a deeper insight into the reaction intermediates defining the stereochemistry of the exocyclic double bond, the different behavior of secondary vs. tertiary carboxylates, and a potential chirality transfer in this process, we performed DFT calculations on model gold(I)-complex **XI**.[23]

3.3.1 Allenyl acetate formation

Au(I)-complex of (*S*)-4-((1*R*,2*S*)-2-vinylcyclopropyl)but-3-yn-2-yl acetate **XIa** reacts through $\mathbf{TS_{XIa\text{-}XIIa}}$($\Delta H^{\neq}$ = 6.5 kcal/mol) and $\mathbf{TS_{XIIa\text{-}XIIIa}}$($\Delta H^{\neq}$ = 2.8 kcal/mol) to give gold coordinated allene **XIIIa** in a reversible and slightly endothermic process (ΔH = 0.4 kcal/mol) (Scheme 8).[24] **XIIIa** shows a clear "allene" character, with gold coordinated to the more external double bond and the four allenyl substituents disposed perpendicularly resembling the gold-coordinated minimized structures of simple allenes **20a-d** (Scheme 6). **XIIIa** is in equilibrium with a more cationic-type derivative **XIVa** through $\mathbf{TS_{XIIa\text{-}XIVa}}$($\Delta H^{\neq}$ = 3.4 kcal/mol) thermodynamically more stable (ΔH = - 4.0 kcal/mol), where the internal double bond is now activated leaving the gold almost exclusively coordinated to the central carbon atom of the allene.[25] From **XIIIa**, the formation of an *E*-configured vinyl gold derivative **XIVd** can be also envisioned although, for the sake of clarity, only **XIIIa** will be considered here (a complete version of Scheme 8 summarizing all possible isomers can be found in the Supporting Information).[26] The stereochemical information of the acetate at the propargylic position is lost by a low barrier transition state $\mathbf{TS_{XIVa\text{-}XIVb}}$($\Delta H^{\neq}$ = 3.1 kcal/mol), which converts **XIVa** into its enantiomer **XIVb** in a slightly exothermic transformation (ΔH = -0.7 kcal/mol). On the other hand, **XIVb** could also arise from **XIb** in an analogous manner to the one described above. Such epimerization event is well precedented experimentally,[27] and was recently studied by the groups of Malacria[25] and Toste.[13b, 19]

Scheme 8. Reaction coordinate diagram for the [3,3]-acetoxy migration of **XIa** to cationic intermediate **XIVa-b**. Calculations at the B3LYP/6-31G(d) (C, H, O, P), LANL2DZ (Au) level (+ ZPE corrected energies are given in kcal/mol). Au = (IPr)Au

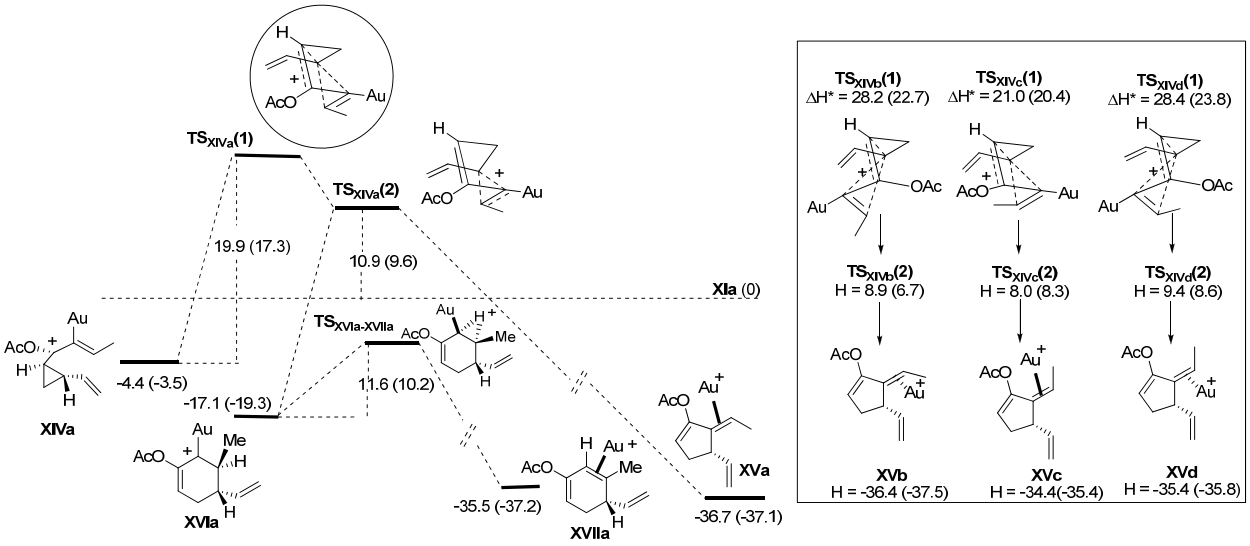


3.3.2 Cyclization step

The next step along the reaction coordinate involves the cyclopropyl ring opening and C-C bond formation to give the cyclopentannulation products. The parallel reactions of the four isomers **XIVa-d** were computed although, for the sake of clarity, only the structures of intermediates derived from **XIVa** are explicitly shown (Scheme 9, left). The relative energies for the other isomers (**XIVb**: epimer at the carbon bearing the acetate, **XIVc-d**: *E* vinyl gold isomers, respectively) have been summarized in the right part of Scheme 9. Thus, from **XIVa** two adjacent transition states, one higher in energy: $\mathbf{TS_{XIVa}(1)}$ ($\Delta H^{\neq}$ = 19.9 kcal/mol) and a second one laying lower in the reaction profile: $\mathbf{TS_{XIVa}(2)}$ ($\Delta H^{\neq}$ = 10.9 kcal/mol) were found to deliver cyclopentene acetate **XVa** without an intervening intermediate.[28] Interestingly, $\mathbf{TS_{XIVa}(1)}$ can be described as a gold-stabilized nonclassical carbocation related to those proposed in Scheme 2. [13a,29] On the other hand, $\mathbf{TS_{XIVa}(2)}$ constitutes a "bifurcation point" in the reaction profile, which can evolve either to cyclopentenyl **XVa** or towards a 6-membered ring **XVIa**, although formation of **XVa** is thermodynamically much more favorable ($H_{\mathbf{XVa}}$ = -36.7 vs. $H_{\mathbf{XVIa}}$ = -17.1 kcal/mol). The product of a *β*-hydride elimination in **XVIa** would yield cyclohexadiene **XVIIa**, which was never detected experimentally.

Solvent effects (CH_2Cl_2) were considered in these calculations (energy values in brackets in Scheme 9). As expected, the energy of all **TS(1)** is lower than in the gas phase since the stabilization of the carbocation retards the cyclopropyl ring opening and promotes the formation of the cycle. More importantly though, the energies of all **TS(1)** are still higher than those of **TS(2)**, so that the first step remains the rate-limiting step, thus governing the stereochemistry of the exocyclic olefin.

Scheme 9. Reaction coordinate diagram for the cyclopentannulation of **XIVa**. Calculations at the B3LYP/6-31G(d) (C, H, O, P), LANL2DZ (Au) level (+ ZPE corrected energies are given in kcal/mol. Values in brackets are considering solvent effects (CH_2Cl_2)). Au = (IPr)Au



Since the stereochemistry observed in the exocyclic olefin of cyclopentene acetates **7** seems to be under kinetic control,[16] transition states $\mathbf{TS_{XIVa\text{-}d}(1)}$, higher in energy than $\mathbf{TS_{XIVa\text{-}d}(2)}$, were closely examined. In $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVc}(1)}$, we observe that the configuration at C_6 of the cyclopropyl ring forces an "endo" reaction, where the Au-C bond is always oriented towards the cyclopropyl ring, whereas $\mathbf{TS_{XIVb}(1)}$ and $\mathbf{TS_{XIVd}(1)}$, higher in energy, present an "exo" approach, where the cyclization takes place from the opposite side of the cyclopropyl ring (Scheme 9). $\mathbf{TS_{XIVa\text{-}d}(1)}$ shows an early carbocation being formed at C_6 with the cyclopropyl unit almost intact. The δ^+ developing in the incipient carbocation interacts with the electron-rich vinyl gold forming a *pseudo*-6-membered ring cycle in a boat conformation (Figure 1).

In the two transition states of lower energy, $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVc}(1)}$, the substituents at C_1 and the terminal carbon atom of the double bound C_6 are eclipsed. This unfavorable eclipsing interaction is enhanced in $\mathbf{TS_{XIVc}(1)}$, where methyl and vinyl groups are in pseudo-axial positions (Figure 1, right upper row). Therefore, for each couple, the transition states displaying the Au and Me in "syn" disposition have a lower activation energy than those with both groups in "*trans*" ($\mathbf{TS_{XIVa}(1)} < \mathbf{TS_{XIVc}(1)}$ and $\mathbf{TS_{XIVb}(1)} < \mathbf{TS_{XIVd}(1)}$). These observations led us to conclude, that the lower energy reaction path transits from **XIVa** via $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVa}(2)}$ yielding (*E*)-cyclopentenyl acetate **XVa** as a major product under kinetic control although the *E* product (**XVa**) is also thermodynamically more stable than **XVc**.[16]

The stabilizing effect of the vinylic (or aromatic) substituent by delocalization of the δ^+ generated upon cyclopropyl ring opening can be easily rationalized looking at the key C-C distances in the transition states. In fact the C_6-C_7 and the C_7=C_8 distances measured in **XIa** and **XIVa** are 1.48 Å, 1.47 and 1.33 and 1.34 Å respectively. In contrast, in $\mathbf{TS_{XIVa(1)}}$, the distances reflect a more allylic character of the vinyl moiety with 1.42 and 1.36 Å values. Furthermore, the NBO analysis of $\mathbf{TS_{XIVa(1)}}$, shows a strong interaction (63.8 kcal/mol) between the π-orbital of the double bond and the empty developing orbital on C_6, which is not present neither in **XIa** nor in **XIVa**. This strong interaction is also reflected in the analysis of the partial charges, which shows

an increasing positive charge (+0.2 e) in the vinyl moiety of the $\mathbf{TS_{XIVa(1)}}$ *vs.* the value measured in **XIa** (+0.06 e).

In the second transition states ($\mathbf{TS_{XIVa}(2)}$, $\mathbf{TS_{XIVc}(2)}$) a complete rupture of the cyclopropyl ring can be observed, with the fully developed carbocation in close interaction with the metal-vinyl bond ($\mathbf{TS_{XIVa}(2)}$: dC_2-C_6 = 2.0 Å vs. $\mathbf{TS_{XIVc}(2)}dC_2$-$C_6$ = 1.953 Å) (Figure 1, lower row). The four carbon atoms C_1-C_2-C_5-C_6 are coplanar and in contrast with steric interactions analyzed for $\mathbf{TS_{XIVa}(1)}$ vs. $\mathbf{TS_{XIVc}(1)}$, the stronger steric congestions occurs between vinyl and methyl groups in $\mathbf{TS_{XIVa}(2)}$ disfavoring it compared to $\mathbf{TS_{XIVc}(2)}$ (Figure 1). Nevertheless, since these are the lower energy transition states in the reaction coordinate, they have no influence in the structure of the final products. Solvent effects also influence the key C-C distances (C_1-C_2, C_1-C_6, C_2-C_6, Au-C_2), which are a bit shorter in the gas phase (Figure 1).

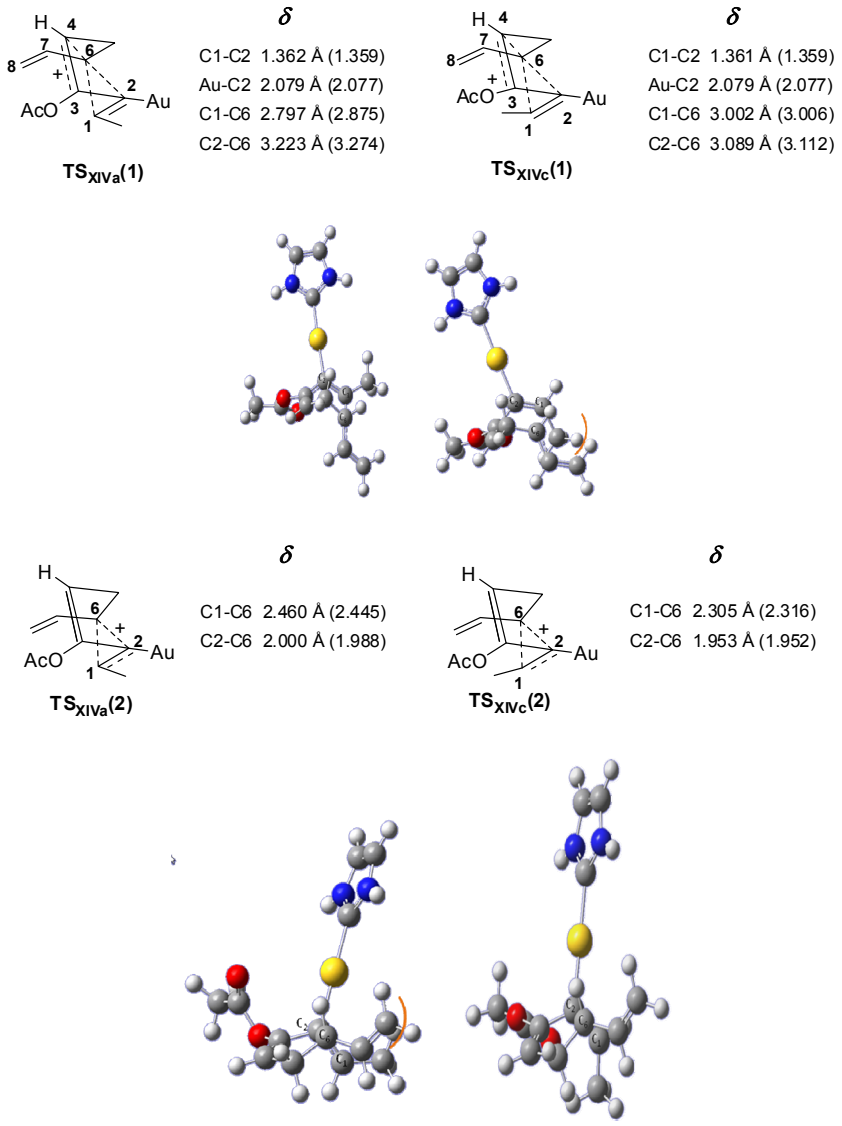


Figure 1. Upper row: structures of transition states $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVc}(1)}$ highlighting the interaction between the cyclopropyl ring and the vinyl gold moiety and the eclipsed interaction between substituents C_1 and C_6 and relevant distances (in brackets considering solvent effect). Lower row: structures of transition states $\mathbf{TS_{XIVa}(2)}$ and $\mathbf{TS_{XIVc}(2)}$ highlighting the steric

interaction between methyl at C_1 and vinyl at C_6 and relevant distances (in brackets considering solvent effect). Au = (IPr)Au

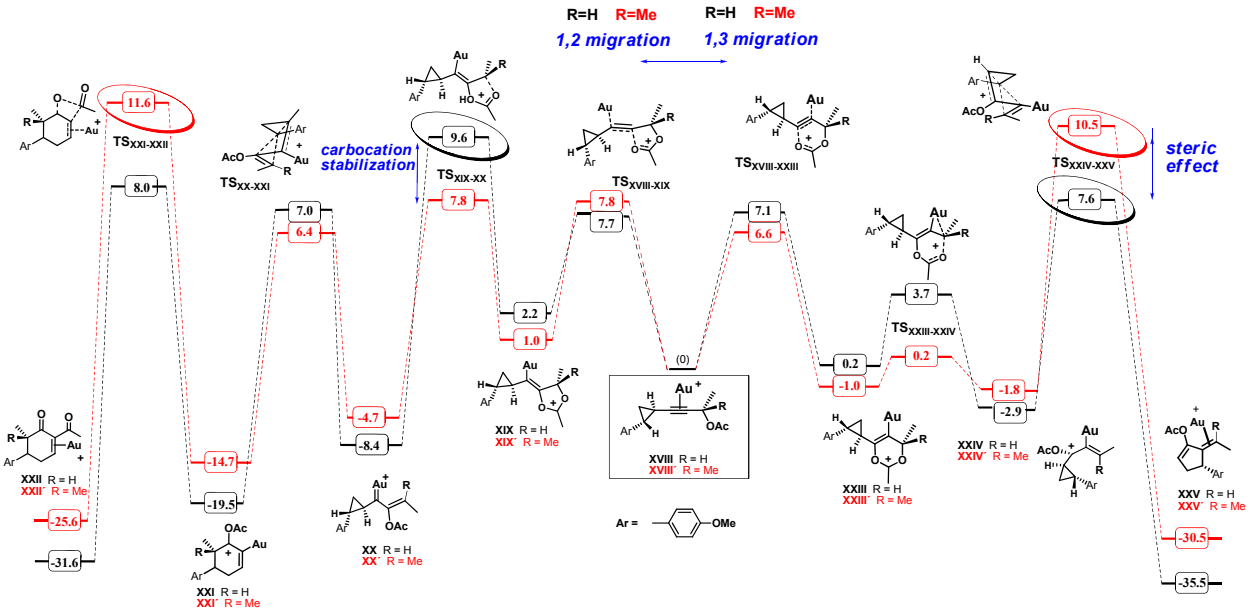
3.3.3 1,2- vs. 1,3-Acyloxy Migration

The results obtained with tertiary acetates and [(IPr)Au(NTf_2)] (Schemes 4 and 5), where products presumably arising from both 1,2- and 1,3-acyloxy migration paths could be isolated, prompted us to study this mechanistic dichotomy more in depth. Previous work in this area has shown how minimal changes in the structure of starting materials, catalysts, etc… can play a key role in the preference for one of these two reaction manifolds.[8] Our computational models were the IPrAu-complexes of (*S*)-4-((1*R*,2*S*)-2-*p*-methoxyphenylcyclopropyl)but-3-yn-2-yl acetate (**XVIII**) and 2-methyl-4-((1*R*,2*S*)-2-*p*-methoxyphenylcyclopropyl)but-3-yn-2-yl acetate (**XVIII´**) respectively (Scheme 10).

For secondary acetate **XVIII** (route in black), the reaction coordinate following a 1,2-acetoxy migration (left path) has in $\mathbf{TS_{XIX\text{-}XX}}$ the higher energy barrier ($\Delta H^{\neq}$ = 9.6 kcal/mol) whereas the 1,3-migration (right path) proceeds smoothly by the previously described intermediates, with lower activation energy for the determining step $\mathbf{TS_{XXIV\text{-}XXV}}$ ($\Delta H^{\neq}$ = 7.6 kcal/mol), which can explain that no products derived of a 1,2-acetoxy migration were found in the reaction of secondary acetates.

In sharp contrast, for tertiary acetate **XVIII´** (route in red) the steric hindrance caused by the presence of two methyl groups at the propargylic position raises the activation energy along the 1,3 migration pathway (right path) to almost 10.5 Kcal/mol for $\mathbf{TS_{(XXIV\text{-}XXV)}}$. This barrier is now comparable to the energy needed in the 1,2-migration path via $\mathbf{TS_{(XXI\text{-}XXII)}}$ (11.6 Kcal/mol). Since the system can be considered under Curtin-Hammet conditions (from **XVIII´** to **XXI´**-**XXIV´**), the product composition will depend on the difference in energies between the respective transition states ($\Delta\Delta H^{\neq}$ = 1.1 kcal/mol) thus becoming competitive. It is important to mention that, as shown in Scheme 5, products arising from the cyclopropyl ring opening of **XVIII´** have been isolated in the reaction, which has never been the case for the secondary acetate derivatives **XVIII**.

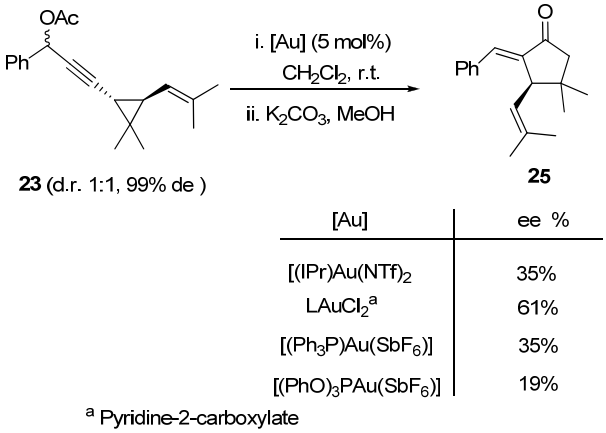
Scheme 10. Reaction coordinate diagrams for the 1,2- vs. 1,3-acyloxy migration of secondary vs. tertiary propargyl acetates. Calculations at the B3LYP/6-31G(d) (C, H, O), LANL2DZ (Au) level (+ ZPE corrected energies are given in kcal/mol). Au = (IPr)Au



3.4 Chirality transfer

The interesting issue of a possible chirality transfer in these systems was addressed both experimental and computationally. Optically active substrates **23** and **24** were prepared from (1*R*,3*R*)-(-)-*trans*-chrysanthemum acid (99% ee) (Scheme 11).[26]

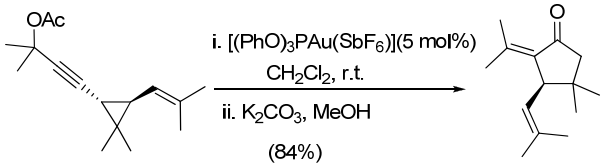
Scheme 11. Chirality transfer of compounds **23** and **24**



23 (d.r. 1:1, 99% de) **25**

[Au]	ee %
[(IPr)Au(NTf)$_2$	35%
LAuCl$_2$[a]	61%
[(Ph$_3$P)Au(SbF$_6$)]	35%
[(PhO)$_3$PAu(SbF$_6$)]	19%

[a] Pyridine-2-carboxylate

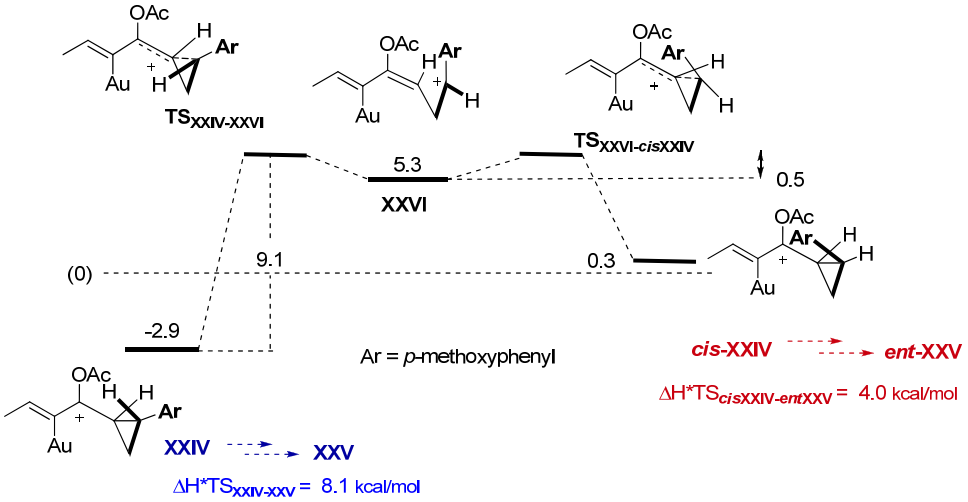


24 (ee > 99%) **26** (50 % ee)

In sharp contrast with our previous results obtained with 1-cyclopropyl-propargyl acetates,[13a] the cycloisomerization of **23** (dr = 1:1, 99% de) under standard conditions with different catalytic systems afforded, after methanolysis, cyclopentanone **25** in 61% ee in the best case using pyridine-2-carboxylate gold(III) catalyst. A similar behavior was observed for tertiary acetate **24**, which upon treatment with $[(PhO)_3PAu(SbF_6)]$ (5 mol%) and methanolysis, afforded **26** in only 50% ee.[30]

These results, prompted us to re-examine our mechanistic proposal for these cycloisomerizations. According to the calculations presented in Scheme 9, the reaction is stereospecific since the ring-opening of the cyclopropyl via gold-stabilized carbocations $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVa}(2)}$ takes place with retention of the configuration, which in principle, should be translated in the final products. A careful ^{1}H-NMR analysis of the reaction of *trans*-**5k** in the presence of $[(IPr)Au(NTf_2)]$ or pyridine-2-carboxylate gold (III) showed that in addition to the expected scrambling at the propargylic position as predicted in Scheme 8,[31] a partial epimerization at the cyclopropyl occurred prior to the cyclization event.[26] A computational study revealed a reaction pathway that could account for such configurational instability (Scheme 12).[26]

Scheme 12. Reaction coordinate diagrams for the cyclopropyl epimerization at of **XXIV**. Calculations at the B3LYP/6-31G(d) (C, H, O), LANL2DZ (Au) level (+ ZPE corrected energies are given in kcal/mol; calculations considering solvent effects (CH_2Cl_2)). Au = (IPr)Au



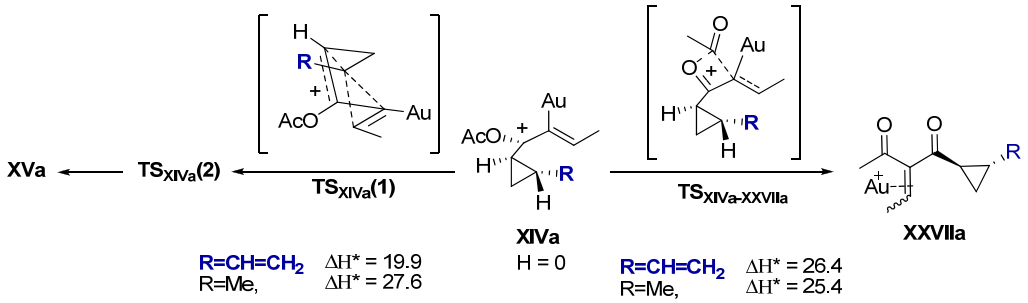
First, **XXIV** can undergo a cyclopropyl ring-opening via $\mathbf{TS_{XXIV\text{-}XXVI}}$ to give a high energy intermediate **XXVI**. The process is endothermic due to the intrinsic unstable nature of such purely carbocationic intermediate even if the calculation takes into account solvent effects (ΔH = 8.2 kcal/mol). Upon C-C rotation via $\mathbf{TS_{XXVI\text{-}\textit{cis}XXIV}}$, the minor isomer ***cis*-XXIV** is formed. The activation barriers to transform **XXIV** into ***cis*-XXIV** are comparable to those obtained for the cyclopentannulation process and summarized in Scheme 10. Therefore, we have to assume that even if the cycloisomerization is an intrinsically stereospecific process, a competitive epimerization at the cyclopropyl moiety can erode the chirality transfer of these transformations. To understand the loss of chirality by such mechanism, **XXIV** should be in equilibrium with cyclopropyl propargyl acetate **XVIII** (or analogously, **XIVa** with **XIa**), which seems to be the case according to the energy barriers summarized in Schemes 8 and 10). A final requirement involves the transformation of ***cis*-XXIV** into the final cyclopentenyl acetate ***ent*-XXV**, which seems to be possible according to the $\Delta H^{\neq}$ values obtained for that process, comparable to the

ones obtained for the *trans* product ($\Delta H^{\neq}$ $\mathbf{TS_{XXIV\text{-}XXV}}$ = 8.1 vs. $\Delta H^{\neq}$ $\mathbf{TS_{\textit{cis}XXIV\text{-}\textit{ent}XXV}}$ = 4.0 kcal/mol, considering solvent effects in both cases).

3.4.1 Acetate Fission vs. Cyclopropyl Ring Opening

Finally, from intermediates of type **XIVa**, we decided to study the competitive acetate fission process to give *α*-ylidene-*β*-diketones **XXVIIa** as previously described by Zhang and co-workers.[14] The activation energy for the attack of metal vinyl bond into the acetate $\mathbf{TS_{XIVa\text{-}XXVIIa}}$ is aprox. 25-26 kcal/mol, independently of the substituent at the cyclopropyl ring (Scheme 13, right). However, the activation barrier for the ring opening of the methyl-substituted cyclopropyl rises to more than 27.6 kcal/mol (vs. 19.9 kcal/mol for the vinyl substituted one) thus highlighting the importance of the cyclopropyl substituent in the reaction mechanism (Scheme 13, left).

Scheme 13. Reaction coordinate diagrams for the cyclopentannulation vs. the acetate fission reaction. Calculations at the B3LYP/6-31G(d) (C, H, O, P), LANL2DZ (Au) level (+ ZPE corrected energies are given in kcal/mol). Au = (IPr)Au



3.5 Conclusion

We present here a complete study on the reactivity of 3-cyclopropyl propargylic acetates and enol ethers with Au(I) and Au(III) catalysts. The intelligence gathered in the development of the gold-catalyzed homo-Rautenstrauch rearrangement previously reported by our group aided the selection of substituents at the cyclopropyl ring able to tune the reactivity of these settings in favor of a cyclopentannulation vs. an acetate fission process to give *α*-ylidene-*β*-diketones. Supported by DFT calculations, this study sheds light on the key gold-stabilized "nonclassical carbocationic" intermediates involved the stereocontrolled synthesis of 5-(*E*)-alkylidene-cyclopentenyl acetates and reveals the intrinsic stereoespecific nature of these transformations. Further experimental and computational evidence are disclosed to explain the lack of a complete chirality transfer in optically active settings: the cyclopentannulation process competes with a gold-triggered cyclopropyl opening/closure prior to the cyclization event. Surprisingly, such cyclopropyl scrambling has been found for both *cis* and *trans*- settings thus highlighting the configurational promiscuity of these motifs. The rearrangement of tertiary acetates has been highly illuminative of the competitive nature of the 1,2- and 1,3-acyloxy migration pathways, opening the venue for new transformations orchestrated in that regard, which is currently being pursued and will be reported in due course.

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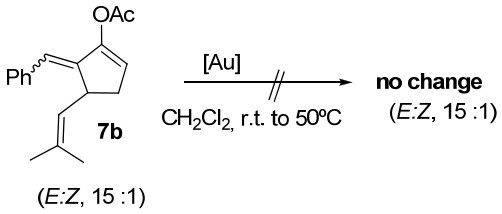
[12] With Au: (a) Huang, X.; de Haro, T.; Nevado, C. *Chem. Eur. J.* **2009**, *15*, 5904-5908. (b) Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740-3741. With Pt, see: (c) Ji, K.-G.; Shu, X.-Z.; Chen, J.; Zhao, S.-C.; Zheng, Z.-J. ; Lu, L. ; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2008**, *10*, 3919-3922. (d) Cho, E. J.; Lee, D. *Adv. Synth. Catal.* **2008**, *350*, 2719-2723. For Ru, see: (e) Ohe, K.; Fujita, M.; Matsumoto, H.; Tai, Y.; Miki, K. *J. Am. Chem. Soc.* **2006**, *128*, 9270-9271.

[13] (a) Zou, Y.; Garayalde, D.; Wang, Q.; Nevado, C.; Goeke, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 10110-10113. For a related study, see also: (b) Mauleón, P.; Krinsky, J. L.; Toste, D. F. *J. Am. Chem. Soc.* **2009**, *131*, 4513-4520.

[14] Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414-8415.

[15] The *E*-configuration of the major isomer was assigned based on NOE studies.

[16] Compound **7b** was treated with catalytic amounts of $IPrAuNTf_2$, $LAuCl_2$ (L = pyridine-2-carboxylate) and $Ph_3PAuNTf_2$ at room temperature and at 50 ºC without any remarkable change in the isomeric ratio of the exocyclic alkene.



[17] (a) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814-1815. (b) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598-12599.

[18] (a) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nature* **2009**, *1*, 482-486. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378.

[19] (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978-15979. (b) Benjamin D. S.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132-8133.

[20] (a) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925-3927. (b) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151-2153.

[21] Longer reaction times and the Au-catalyst seem to be crucial for this somewhat unexpected isomerization which is currently the focus of further mechanistic studies.

[22] (a) Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207-2209. (b) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993-3006. (c) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 909-911. (d) Lee, J. H.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 912-914.

[23] Calculations performed with Gaussian ´03 (full reference in the Supporting Information).

[24] Alternatively, a double 1,2- migration of the acetoxy moiety could also explain the formation of allenyl intermediate **XIV**. For an in depth study on this possibility, see ref. 8.

[25] Gandon, V.; Lemière, G.; Hours, A.; Fensterbank, L, Malacria, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7534-7538.

[26] Further details can be found in the Supporting Information.

[27] Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875-944.

[28] $\mathbf{TS_{XIVa}(1)}$ and $\mathbf{TS_{XIVa}(2)}$ form a two-step no-intermediate system. For related examples, see: Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 1319-1328.

[29] (a) Olah, G.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69-95. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863-11869. (c) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am.*

Chem. Soc. **2005**, *127*, 8244-8245. (d) Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed*. **2008**, *47*, 5030-5033.

[30] The absolute configuration shown here for the cyclopentenone products was proposed based on our previous results on the cyclization of 1-cyclopropyl propargyl acetates (ref. 13a).

[31] In ref. 13b Toste et. al. have shown that scrambling in the *cis*-1-cyclopropyl-propargyl acetates at both propargylic and cyclopropyl positions takes place before the cyclization is complete. However, no such phenomenon was detected for the *trans*-cyclopropyl derivatives they studied nor the responsible intermediates for the second of these processes could be fully characterized computationally.

Chapter 3

Experimental Section

Contents:

1. General information

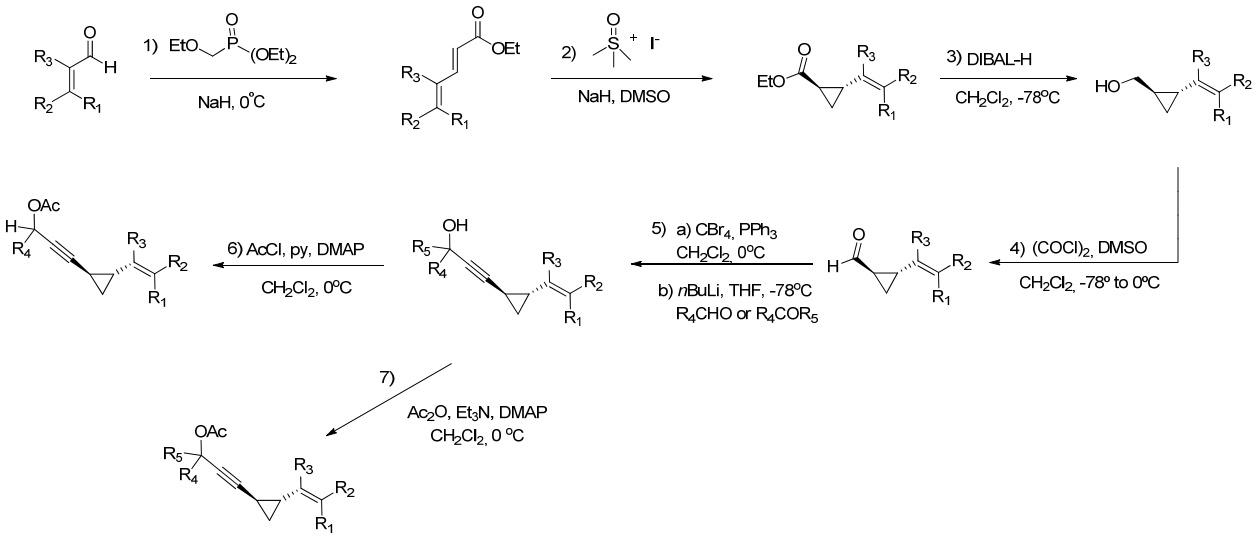
All reactions were carried out under a nitrogen atmosphere using Standard Schlenk techniques. All reagents were used as received unless otherwise noted. Solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silacycle silica gel (230-400 mesh). NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual 1H and 13C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), doublet-doublet-doublet (ddd), quintet (quint), septet (sept), multiplet (m), and broad (br). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer. 10 spectra were acquired. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 <l PEG200, 2 <l PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100ml MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard. HPLC was performed on Waters 600 instrument using 4.6 x 25 cm Chiralpack IB and Chiralcel OD-H columns. $[\alpha]_D$ values were recorded on JASCO P-2000 Polarimeter. IPrAuNTf$_2$[1] and dichloro(pyridine-2-carboxylato)gold(III) complex[2] were prepared according to previously reported procedures.

[1] Ricard, L.; Gagosz, F. *Organometallics* **2007**, 26, 4704-4707.

[2] Dar, A.; Moss, K.; Cottrill, S. M.; Parish, R. V.; McAuliffe, C. A.; Pritchard, R. G.; Beagley, B.; Sandbank, J. *J Chem. Soc., Dalton Trans.* **1992**, 1907-1913.

2. Preparation and characterization of 3-cyclopropyl propargyl acetates and cyclization products. Complementary Table 2.

2.1 General procedure for the preparation of 3-cyclopropyl propargyl acetates



1) To a solution of NaH (1.05 equiv.) in THF (0.8 M) at 0 °C, triethyl phosphonoacetate (1.1 equiv.) was added dropwise. The mixture was stirred at 0 °C for 20 minutes. Then, the aldehyde (1.0 equiv.) was added dropwise at 0 °C. The reaction was stirred at room temperature for 12 hours and quenched with brine. The volume was reduced to the 1/3 under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (Pentane) to give the corresponding (*E*)-*α,β*-unsaturated ester in 82-95% yield.
2) To a solution of NaH (1.05 equiv.) in THF (0.6 M) at room temperature, trimethylsulfoxonium iodine (1.15 equiv.) was added as a solid in small portions. The mixture was stirred for 1 hour before a solution of the corresponding ester (1.0 equiv.) in DMSO (1.0 M) was added. The mixture was stirred at room temperature for 12 hours. The reaction was quenched with brine and extracted several times with diethyl ether. The organic layers were dried over Na_2SO_4. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (Pentane) to give the corresponding cyclopropyl ester derivate in 62-90% yield.
3) To a solution of the corresponding cyclopropyl ester (1.0 equiv.) in CH_2Cl_2 (0.2 M) at -78 °C, DIBAL-H (1.0 M in hexane, 2.2 equiv.) was added dropwise. The reaction was stirred at -78 °C for 1 hour. The reaction was quenched with ethyl acetate (3 equiv.) and diluted with diethyl ether. A saturated solution of Na/K-tartrate was added to the mixture and the

reaction was stirred for another 3 hours till clear separation of the two phases was observed. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (Hexane:AcOEt 4:1) to give the corresponding alcohol in 60-90% yield.

4) To a solution of oxalyl chloride (1.5 quiv.) in CH_2Cl_2 (0.4 M), DMSO (2.3 equiv.) was added dropwise. The reaction was stirred at -78 ^oC for 1 hour. Then, the corresponding alcohol was added (1.0 equiv) dropwise in CH_2Cl_2 (1.4 M). The reaction was stirred at -78 ^oC for 1 hour, and triethylamine (5.0 quiv.) was added dropwise and the reaction was stirred at -78 ^oC for another hour. The mixture was warmed up to room temperature for another 30 minutes and quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was used in the next step without further purification.
5) To a solution of CBr_4 (2.2 equiv.) in CH_2Cl_2 (1.5 M) at 0 ^oC, a solution of triphenylphosphine (4.4 equiv.) in CH_2Cl_2 (1.5 M) was added dropwise. The resulting dark orange solution was stirred for 5 minutes. A solution of the corresponding cyclopropylaldehyde (1.0 equiv.) dissolved in CH_2Cl_2 (1.0 M) was added dropwise. The solution was stirred at 0 ^oC for 2-3 hours. The reaction mixture was quenched by addition of water. The aqueous layers where extracted with CH_2Cl_2. The combined organic layers were washed with water and brine. The organic layer was dried over $MgSO_4$ and the crude was purified by column chromatography on silica gel (Hexane) to yield the dibromo derivatives in 65-80% yield.

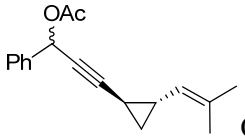
   To a solution of the corresponding cyclopropyl-dibromo derivate (1.0 equiv.) in THF (0.2 M) at -78 ^oC, *n*BuLi (1.0 M in hexane, 2.0 equiv) was added dropwise. The solution was stirred at -78 ^oC for 3 hours and then warmed up to room temperature for 20 minutes. The resulting solution was cooled down to -78 ^oC and the aldehyde (1.05 equiv.) or the ketone (1.05 equiv.) was added dropwise. The reaction was stirred at room temperature for 12 hours. Water was added and the aqueous layer was extracted with EtOAc. The organic layers were dried over Na_2SO_4 and the crude was purified by column chromatography on silica gel (Hexane:EtOAc 25:1) to give the corresponding propargyl alcohol in 33-93% yield.
6) To a solution of the corresponding secondary propargyl alcohol (1.0 equiv.) at 0 ^oC in CH_2Cl_2 (0.4 M), pyridine (20.0 equiv.), DMAP (0.05 equiv.) and AcCl (2.0 equiv.) were sequentially added. The resulting mixture was stirred for 1 hour. The solution was filtered through Celite and the corresponding solution was evaporated under reduced pressure.

The residue was purified by column chromatography on silica gel (Hexane:EtOAc 25:1). The desired secondary propargyl acetates were obtained in 58-97% yield.

7) To a solution of the corresponding tertiary propargyl alcohol (1.0 equiv.) at 0 ^{o}C in CH_2Cl_2 (0.2 M), triethylamine (10.0 equiv.), DMAP (0.1 equiv.) and Ac_2O (5.0 equiv.) were sequentially added. The resulting mixture was stirred for 12 hours. The solution was dried under reduced pressure and the residue was purified by column chromatography on silica gel (Hexane:EtOAc 25:1). The desired tertiary propargyl acetates were obtained in 72-89% yield.

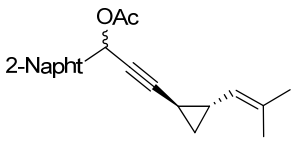
2.2 Characterization of secondary acetates[3]

3-(2-(2-Methylprop-1-enyl)cyclopropyl)-1-phenylprop-2-ynyl acetate (5b)



Obtained as a 1:2 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.49 (m, 2H, major and minor), 7.39-7.32 (m, 3H, major and minor), 6.48-6.46 (m, 1H, minor), 6.45 (d, *J* = 1.6 Hz, 1H, major), 4.94 (dd, *J* = 8.5, 1.2 Hz, 1H, minor), 4.53 (dd, *J* = 8.6, 1.2 Hz, 1H, major), 2.08 (s, 3H, major and minor), 1.84-1.78 (m, 1H, major), 1.75 (s, 3H, major), 1.73 (d, *J* = 0.9 Hz, 3H, minor), 1.71 (d, *J* = 0,9 Hz, 3H, minor), 1.68 (s, 3H, major), 1.65-1.59 (m, 1H, minor), 1.27-1.17 (m, 1H, major), 1.15-1.06 (m, 1H, major), 0.81-0.75 (m, 1H, minor), 0.70-0.62 (m, 1H, minor) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer): δ = 169.8, 137.6, 133.5, 128.7, 128.5, 127.7, 125.1, 90.2, 73.0, 66.1, 25.4, 21.2, 21.1, 18.4, 16.6, 8.6 ppm; (minor isomer): 169.8, 137.6, 134.1, 128.6, 128.4, 127.8, 127.7, 123.1, 88.6, 75.0, 66.1, 25.6, 21.6, 17.7, 16.1, 7.2 ppm; IR (neat, ν/cm^{-1}): 2965, 2915, 2359, 2238, 1680, 1494, 1455, 1369, 1014, 953, 697; MS (ESI) for $C_{18}H_{20}NaO_2^+$ m/z: 291.2 $[M + Na]^+$, 559.2 $[2M + Na]^+$.

3-(2-(2-Methylprop-1-enyl)cyclopropyl)-1-(naphthalene-2-yl)prop-2-ynyl acetate (5c)

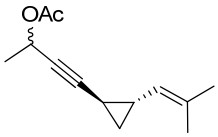


Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (s, 2H), 7.87-7.82 (m, 6H), 7.59 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.52-7.47 (m, 4H), 6.61 (s, 1H), 6.60 (s, 1H), 4.56-4.53 (m, 2H), 2.10 (s, 6H), 1.88-1.80 (m, 2H), 1.75 (d, *J* = 0.9 Hz, 6H), 1.68 (s, 6H), 1.28-1.21 (m, 2H), 1.13-1.08 (m, 2H), 0.82-0.77 (m, 2H)

[3] All racemic starting materials were prepared by cyclopropanation of the corresponding (E)-*α,β*-unsaturated esters. The stereochemistry at the propargylic position was not controlled and therefore mixtures of diastereoisomers were obtained in variable ratios. In some cases, signals of the major and minor isomers separate and the corresponding unambiguous assignment could be done. In other cases, when most of the signals were overlapped, only the signals that separated have been indicated in the ^{13}C-NMR as (2x C).

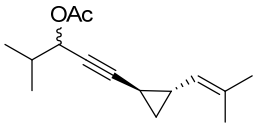
ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 134.9 (2xC), 133.5 (2xC), 133.3, 130.0, 128.4, 128.2, 127.6, 126.9, 126.5, 126.3, 125.1, 90.5 (2xC), 73.1 (2xC), 66.2, 25.4, 21.6 (2xC), 21.2, 18.4, 16.6 (2xC), 8.63, 8.62 ppm; IR (neat, ν/cm^{-1}): 2966, 2921, 2872, 2359, 2335, 2236, 1739, 1442, 1368, 1223, 1014, 856, 817; HRMS (ESI): m/z calcd for $C_{22}H_{22}NaO_2^+$: 341.1520, found: 341.1517.

4-(2-(2-Methylprop-1-enyl)cyclopropyl)but-3-yn-2-yl- acetate (5d)



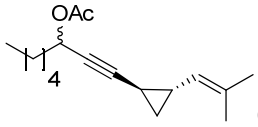
Obtained as a 1:1.5 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47-5.40 (m, 1H, major and minor), 4.92 (d, *J* = 9.0 Hz, 1H, minor), 4.52 (d, *J* = 8.9 Hz, 1H, major), 2.05 (s, 3H, major and minor), 1.75 (s, 3H, major), 1.75 (s, 3H, minor), 1.73 (s, 3H, minor), 1.67 (s, 3H, major), 1.56-1.53 (m, 1H, major), 1.45 (d, *J* = 6.4 Hz, 3H, minor), 1.43 (d, *J* = 6.4 Hz, 3H, major), 1.21-1.11 (m, 2H major, 1H minor), 1.07-1.01 (m, 2H, minor), 0.77-0.72 (m, 1H, major), 0.63-0.56 (m, 1H, minor) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer): δ = 169.9, 133.4, 125.2, 87.5, 74.9, 60.9, 25.4, 21.8, 21.5, 21.2, 18.4, 16.5, 8.4 ppm, (minor isomer): 169.9, 133.8, 122.9, 85.8, 74.9, 60.9, 25.7, 21.7, 21.1, 18.4, 17.4, 16.0, 7.0 ppm; IR (neat, ν/cm^{-1}): 2986, 2968, 2934, 2872, 2238, 1739, 1447, 1370, 1231, 1042, 945, 847; HRMS (ESI): m/z calcd for $C_{13}H_{18}NaO_2^+$: 229.1205, found: 229.1204.

4-Methyl-1-(2-(2-methylprop-1-enyl)cyclopropyl)pent-1-yn-3-yl acetate (5e)



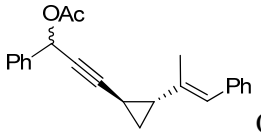
Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.20 (dd, *J* = 5.6, 0.7 Hz, 1H), 5.18 (dd, *J* = 5.6, 0.7 Hz, 1H), 4.54-4.51 (m, 2H), 2.07 (s, 6H), 1.98-1.90 (m, 2H), 1.79-1.73 (m, 2H), 1.74 (m, 6H), 1.67 (s, 6H), 1.19-1.14 (m, 2H), 1.06-1.01 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 6H), 0.95 (d, *J* = 6.7 Hz, 6H), 0.77-0.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 133.4, 125.3 (2xC), 88.7, 72.5 (2xC), 69.5, 32.6, 25.4, 21.6 (2xC), 21.1, 18.4, 18.2, 17.5, 16.6 (2xC), 8.5 ppm; IR (neat, ν/cm^{-1}): 2965, 2930, 2874, 2235, 1741, 1468, 1447, 1371, 1232, 1018, 978, 848; HRMS (EI): m/z calcd for $C_{15}H_{22}O_2^+$: 234.1614, found 234.1620.

1-(2-(2-Methylprop-1-enyl)cyclopropyl)oct-1-yn-3-yl acetate (5f)



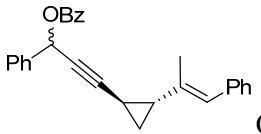
Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34 (t, *J* = 6.6 Hz, 1H), 5.33 (t, *J* = 6.6 Hz, 1H), 4.52 (dq, *J* = 1.4, 8.9 Hz, 2H), 2.06 (s, 6H), 1.78-1.65 (m, 4H), 1.75 (m, 6H), 1.67 (s, 6H), 1.44-1.36 (m, 4H), 1.34-1.25 (m, 10H), 1.19-1.14 (m, 2H), 1.06-1.01 (m, 2H), 0.89 (t, *J* = 7.0 Hz, 6H), 0.77-0.72 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 133.4 (2xC), 125.2 (2xC), 88.1, 74.0 (2xC), 64.6, 35.1, 31.3, 25.4, 24.7, 22.5, 21.6, 21.1, 18.4, 16.6, 13.9, 8.5 (2xC) ppm; IR (neat, ν/cm^{-1}): 2955, 2929, 2860, 2237, 1741, 1455, 1371, 1232, 1018, 954; HRMS (ESI): m/z calcd for $C_{17}H_{26}NaO_2^+$: 285.1824, found: 285.1825.

(*E*)-1-Phenyl-3-(2-(1-phenylprop-1-en-2-yl)cyclopropyl)prop-2-ynyl acetate (5g)



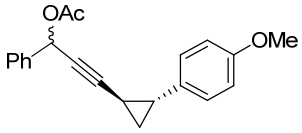
Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.51 (m, 4H), 7.41-7.29 (m, 10H), 7.22-7.18 (m, 6H), 6.48 (s, 1H), 6.47 (s, 1H), 6.35 (s, 2H), 2.11 (s, 6H), 1.99-1.93 (m, 2H), 1.75 (s, 6H), 1.54-1.49 (m, 2H), 1.19-1.09 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 137.8, 137.6, 136.2, 128.8, 128.7, 128.6, 128.1, 127.7, 126.1, 125.3 (2xC), 90.2, 72.9, 66.0, 30.8 (2xC), 21.2, 15.6 (2xC), 14.7 (2xC), 7.2 ppm; IR (neat, ν/cm^{-1}): 3062, 3026, 2926, 2864, 2362, 2335, 2237, 1738, 1493, 1455, 1396, 1224, 1014, 952, 740, 697; HRMS (ESI): m/z calcd for $C_{23}H_{22}NaO_2^+$: 353.1521, found: 353.1517.

(*E*)-1-Phenyl-3-(2-(1-phenylprop-1-en-2-yl)cyclopropyl)prop-2-ynyl benzoate (5h)



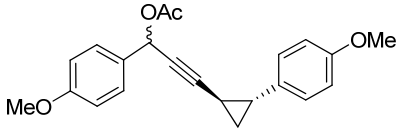
Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10-8.08 (m, 4H), 7.62-7.60 (m, 4H), 7.58-7.54 (m, 2H), 7.45-7.36 (m, 10H), 7.32-7.29 (m, 4H), 7.21-7.16 (m, 6H), 6.72 (s, 1H), 6.71 (s, 1H), 6.35 (s, 2H), 2.00-1.94 (m, 2H), 1.74 (d, *J* = 1.3 Hz, 6H), 1.55-1.50 (m, 2H), 1.19-1.09 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 137.8, 137.7, 136.3, 133.1, 130.0, 129.9, 128.8, 128.7, 128.6, 128.3, 128.1, 127.6, 126.1, 125.3, 90.4, 73.0, 66.6, 30.8 (2xC), 15.5 (2xC), 14.7, 7.3 ppm; IR (neat, ν/cm^{-1}): 3062, 3026, 2235, 1723, 1493, 1452, 1384, 1256, 1294, 1093, 1025, 910, 738, 709; HRMS (ESI): m/z calcd for $C_{28}H_{24}NaO_2^+$: 415.1668, found: 415.1668.

3-(2-(4-Methoxyphenyl)cyclopropyl)-1-phenylprop-2-ynyl acetate (5i)



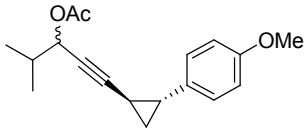
Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.53-7.49 (m, 4H), 7.41-7.34 (m, 6H), 7.03-6.99 (m, 4H), 6.83-6.79 (m, 4H), 6.47 (s, 1H), 6.46 (s, 1H), 3.78 (s, 6H), 2.28-2.23 (m, 2H), 2.10 (s, 6H), 1.53-1.47 (m, 2H), 1.32-1.27 (m, 2H), 1.23-1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.9, 158.2, 137.6 (2xC), 132.4, 128.8, 128.6, 127.7, 127.2 (2xC), 113.9, 90.0, 73.1, 66.1, 55.3, 25.6, 21.2, 17.4, 10.7 (2xC); IR (neat, ν/cm^{-1}): 3035, 2237, 1737, 1514, 1224, 1033, 1014, 951, 912, 747, 697; HRMS (EI): m/z calcd for $C_{21}H_{20}NaO_3^+$ 343.1310, found: 343.1314.

1-(4-Methoxyphenyl)-3-(2-(4-metoxyphenyl)cyclopropyl)prop-2-ynyl acetate (5j)



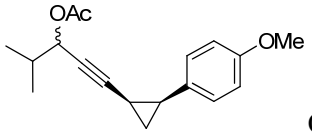
Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.46-7.43 (m, 4H), 7.03-7.00 (m, 4H), 6.91-6.89 (m, 4H), 6.82-6.80 (m, 4H), 6.42 (s, 1H), 6.41 (s, 1H), 3.81 (s, 6H), 3.78 (s, 6H), 2.28-2.23 (m, 2H), 2.08(s, 6H), 1.56-1.47 (m, 2H), 1.32-1.27 (m, 2H), 1.22-1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.9, 160.0, 158.2, 132.5, 129.9, 129.3, 127.2 (2xC), 113.9 (2xC), 89.8, 73.3, 65.8, 55.4, 55.3, 25.7, 21.3, 17.4, 10.8, 10.7; IR (neat, ν/cm^{-1}): 2934, 2835, 2236, 1738, 1611, 1513, 1247, 1227, 1033, 826; HRMS (ESI): m/z calcd for $C_{22}H_{22}NaO_4^+$ 373.1416, found: 373.1412.

1-(2-(4-Methoxyphenyl)cyclopropyl)-4-methylpent-1-yn-3-yl- acetate (5k)



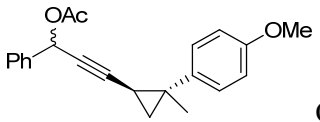
Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.02-6.99 (m, 4H), 6.82-6.79 (m, 4H), 5.22 (d, *J* = 5.6 Hz, 1H), 5.21 (d, *J* = 5.6 Hz, 1H), 3.78 (s, 6H), 2.23-2.17 (m, 2H), 2.09 (s, 6H), 2.00-1.92 (m, 2H), 1.47-1.42 (m,2H), 1.28-1.14 (m, 4H), 0.99 (d, *J* = 10.8 Hz, 6H), 0.98 (d, *J* = 10.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.2, 158.2, 132.6, 127.2 (2xC), 113.8, 88.5, 72.6 (2xC), 69.4, 55.3, 32.6, 25.6 (2xC), 21.1, 18.3, 17.6, 17.4 (2xC), 10.7 (2xC); IR (neat, ν/cm^{-1}): 3445, 2963, 2874, 2360, 1715, 1614, 1515, 1247, 1034, 824; HRMS (ESI): m/z calcd for $C_{18}H_{22}NaO_3^+$ 309.1467, found: 309.1465.

1-(2-(4-Methoxyphenyl)cyclopropyl)-4-methylpent-1-yn-3-yl- acetate (cis-5k)



Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400MHz, CD_2Cl_2) δ = 7.17-7.15 (m, 4H), 6.84-6.81 (m, 4H), 5.01 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.99 (dd, *J* = 5.8, 1.8 Hz, 1H), 3.77 (s, 6H), 2.29-2.23 (m, 2H), 1.97 (s, 6H), 1.77-1.70 (m, 4H), 1.34-1.28 (m, 2H), 1.13-1.07 (m, 2H), 0.75-0.71 (m, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.3, 158.9, 130.4 (2xC), 130.0 (2xC), 113.9 (2xC), 86.5 (2xC), 76.4 (2xC), 69.7 (2xC), 55.8, 32.9 (2xC), 23.3 (2xC), 21.3, 18.3, 17.6 (2xC), 14.6 (2xC), 9.5 (2xC) ppm; IR (neat, ν/cm^{-1}): 3005, 2964, 2933, 2874, 2835, 2237, 1735, 1613, 1514, 1465, 1370, 1230, 1018, 980, 943, 829. HRMS (ESI): m/z calcd for $C_{18}H_{22}NaO_3^+$ 309.1467, found: 309.1461.

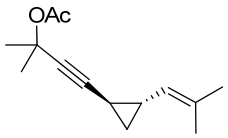
3-(2-(4-Methoxyphenyl)-2-methylcyclopropyl)-1-phenylprop-2-ynyl- acetate (5l)



Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.56-7.54 (m, 4H), 7.42-7.36 (m, 6H), 7.21-7.18 (m, 4H), 6.83-6.81 (m, 4H), 6.51 (s, 3H), 6.50 (s, 3H), 3.78 (s, 6H), 2.11 (s, 6H), 1.67-1.63 (m, 2H), 1.52 (s, 3H), 1.50 (s, 3H), 1.40-1.34 (m, 2H), 0.97-0.92 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.9, 158.0, 137.6 (2xC), 137.5 (2xC), 128.7 (2xC), 128.6, 128.4 (2xC), 127.7, 113.7, 88.5 (2xC), 75.3 (2xC), 66.2, 55.2, 27.3 (2xC), 22.9, 22.8, 21.2, 14.9 (2xC) ppm; IR (neat, ν/cm^{-1}): 3067, 3004, 2956, 2932, 2236, 1736, 1514, 1455, 1369, 1225, 1175, 1032, 904, 727, 649, 548; HRMS (ESI): m/z calcd for $C_{22}H_{22}NaO_3^+$: 357.1458, found: 357.1461.

2.3 Characterization of tertiary acetates

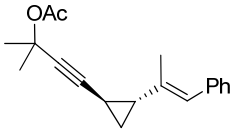
2-Methyl-4-(2-(2-methylprop-1enyl)cyclopropyl)but-3-yn-2-yl acetate (9a)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.97 (dq, *J* = 9.0, 1.1 Hz, 1H, minor), 4.52 (dq, *J* = 8.9, 1.1 Hz, 1H, major), 1.99 (s, 3H, major and minor), 1.77-1.70 (m, 2H, minor), 1.74 (d, *J* = 0.8 Hz, 6H, major), 1.72 (d, *J* = 0.8 Hz, 3H, minor), 1.66 (d, *J* = 0.8 Hz, 3H, minor), 1.63 (s, 3H, minor), 1.62 (s, 3H, minor), 1.61 (s, 6H, major), 1.56-1.51 (m, 1H, minor), 1.17-1.10 (m, 2H, major), 1.04-1.00 (m, 1H, major), 0.74-0.70 (ddd, *J* = 8.5, 5.8, 4.3 Hz, 1H, major), 0.60-0.57 (m, 1H, minor) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer): δ = 169.3, 133.1, 125.4, 86.6,

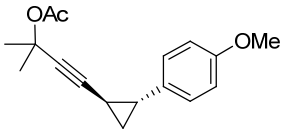
77.6, 72.6, 29.2, 25.4, 22.1, 21.5, 18.4, 16.6, 8.6 ppm, (minor isomer): 169.2, 133.4, 123.3, 85.0, 79.7, 72.5, 29.3, 29.2, 25.6, 22.0, 17.4, 16.1, 7.1 ppm ; IR (neat, ν/cm^{-1}): 2985, 2925, 2362, 2241, 1365, 1240, 1132, 1014, 957, 839; HRMS (ESI): m/z calcd for $C_{14}H_{20}NaO_2^+$: 220.1462, found: 220.1463.

(*E*)-2-Methyl-4-(2-(1-phenylprop-1-en-2-yl)cyclopropyl)but-3-yn-2-yl acetate (9b)



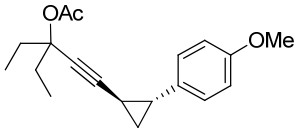
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-7.29 (m, 2H), 7.21-7.16 (m, 3H), 6.35 (s, 1H), 2.02 (s, 3H), 1.92-1.87 (m, 1H), 1.73 (s, 3H), 1.65 (s, 6H), 1.49-1.45 (m, 1H), 1.13-1.03 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 137.8, 136.4, 128.7, 127.9, 125.9, 125.0, 86.5, 77.4, 72.4, 30.6, 29.14, 29.13, 21.9, 15.3, 14.6 ppm; IR (neat, ν/cm^{-1}): 3025, 2985, 2937, 2854, 2237, 1741, 1440, 1365, 1240, 1135, 1124, 1014, 741, 699; HRMS (ESI): m/z calcd for $C_{19}H_{22}NaO_2^+$: 305.1518, found: 305.1517.

4-(2-(4-Methoxyphenyl)cyclopropyl)2-methylbut-3-yn-2-yl acetate (9c)



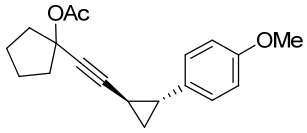
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.01-6.99 (m, 2H), 6.81-6.79 (m, 2H), 3.77 (s, 3H), 2.21-2.16 (m, 1H), 2.01 (s, 3H), 1.64 (s, 6H), 1.47-1.42 (m,1H), 1.26-1.21 (m, 1H), 1.16-1.11 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.4, 158.1, 132.8, 127.1, 113.8, 86.5, 77.7, 72.6, 55.3, 29.2, 25.6, 22.1, 17.6, 10.7; IR (neat, ν/cm^{-1}): 2987, 2938, 2835, 2235, 1739, 1514, 1241, 1179, 1135, 823, 803; HRMS (EI): m/z calcd for $C_{17}H_{20}O_3^+$: 272.1412, found: 272.1413.

3-Ethyl-1-(2-(4-methoxyphenyl)cyclopropyl)pent-1-yn-3yl acetate (9d)



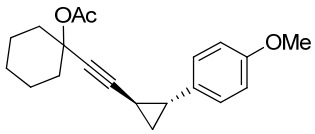
^{1}H NMR (500MHz, $CDCl_3$) δ = 7.02-6.99 (m, 2H), 6.83-6.78 (m, 2H), 3.78 (s, 3H), 2.21-2.16 (m, 1H), 2.06-1.97 (m, 5H), 1.92-1.83 (m, 2H), 1.50-1.45 (m, 1H), 1.26-1.22 (m, 1H), 1.17-1.13 (m, 1H), 0.96 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.4, 158.1, 132.9, 127.1, 113.8, 88.4, 80.5, 75.8, 55.3, 30.9, 25.7, 22.0, 17.7, 10.8, 8.5; IR (neat, ν/cm^{-1}): 2972, 2880, 2237, 1738, 1515, 1459, 1366, 1241, 1036, 831; HRMS (EI): m/z calcd for $C_{19}H_{24}O_3^+$: 300.1725, found: 300.1725.

1-(2-(2-(4-Methoxyphenyl)cyclopropyl)ethynyl)cyclopentyl acetate (9e)



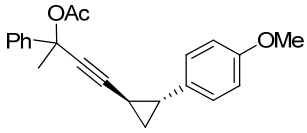
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.02-6.98 (m, 2H), 6.82-6.78 (m, 2H), 3.77 (s, 3H), 2.22-2.15 (m, 3H), 2.11-2.05 (m, 2H), 2.02 (s, 3H), 1.79-1.65 (m, 4H), 1.48-1.43 (m, 1H), 1.25-1.21 (m, 1H), 1.16-1.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.6, 158.1, 132.9, 127.1, 113.8, 87.1, 81.0, 55.3, 40.5, 25.6, 23.3, 21.9, 21.8, 17.6, 10.8; IR (neat, ν/cm^{-1}): 2957, 2247, 1737, 1514, 1244, 906; HRMS (EI): m/z calcd for $C_{19}H_{22}O_3^+$: 298.1569, found: 298.1570.

1-(2-(2-(4-Methoxyphenyl)cyclopropyl)ethynyl)cyclohexyl acetate (9f)



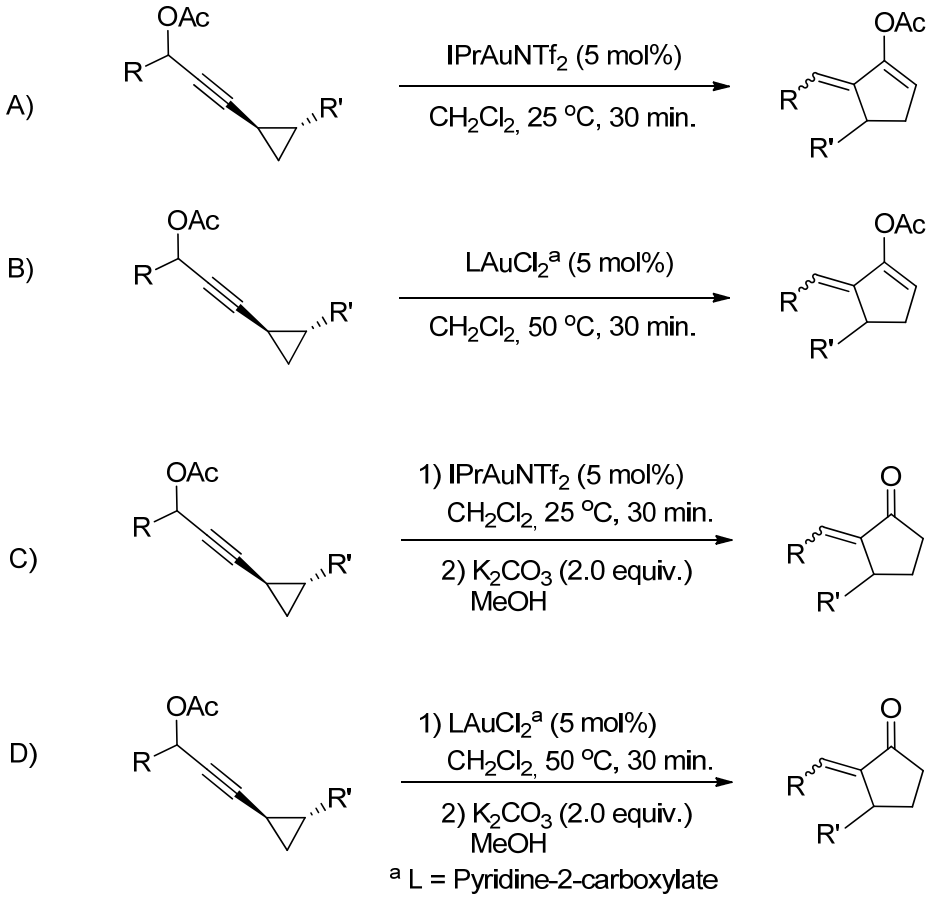
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.02-7.00 (m, 2H), 6.81-6.79 (m, 2H), 3.78 (s, 3H), 2.21-2.17 (m, 1H), 2.10-2.04 (m, 2H), 2.03 (s, 3H), 1.85-1.79 (m, 2H), 1.63-1.56 (m, 4H), 1.52-1.46 (m, 2H), 1.36-1.30 (m, 1H), 1.27-1.22 (m, 1H), 1.17-1.12 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.3, 158.2, 132.9, 127.1, 113.8, 88.7, 76.4, 75.9, 55.3, 37.3, 25.7, 25.3, 22.7, 22.1, 17.8, 10.8; IR (neat, ν/cm^{-1}): 2934, 2858, 1740, 1613, 1514, 1445, 1366, 1229, 1035, 824; HRMS (EI): m/z calcd for $C_{20}H_{24}O_3^+$: 312.1725, found: 312.1723.

4-(2-(4-Methoxyphenyl)cyclopropyl)-2-phenylbut-3-yn-2-yl acetate (9g)



^{1}H NMR (400MHz, $CDCl_3$) δ = 7.57-7.54 (m,2H), 7.37-7.33 (m, 2H), 7.29-7.26 (m, 1H), 7.05-7.03 (m, 2H), 6.86-6.80 (m, 2H), 3.79 (s, 3H), 2.32-2.25 (m, 1H), 2.07 (s, 3H), 1.86 (s, 3H), 1.60-1.53 (m, 1H), 1.36-1.30 (m, 1H), 1.23-1.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.6, 158.2, 143.2, 133.4, 132.7, 128.3, 127.6, 127.2, 124.9, 113.8, 89.9, 76.0, 55.3, 32.3, 25.7, 21.9, 17.7, 10.8; IR (neat, ν/cm^{-1}): 2992, 2934, 2239, 1747, 1514, 1447, 1367, 1236, 1057, 938; HRMS (ESI): m/z calcd for $C_{22}H_{22}NaO_3^+$: 357.1467, found: 357.1471.

2.4 General procedure for the preparation of cyclopent-1-enyl acetates and cyclopentenones from secondary acetates



A) To a solution of the corresponding propargyl acetate (1.0 equiv.) in CH_2Cl_2 (0.05 M), $IPrAuNTf_2$ (0.05 equiv.) was added in one portion. The mixture was stirred at room temperature for 30 minutes. The reaction was quenched with triethylamine (0.05 equiv.). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 50:1) to give the corresponding cyclopent-1-enyl acetates.

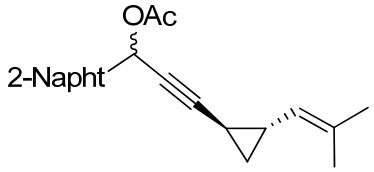
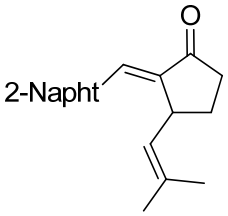
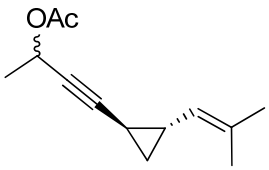
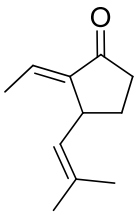
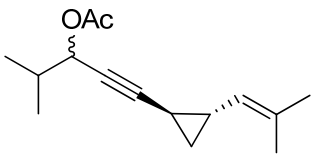
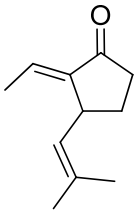
B) To a solution of the corresponding propargyl acetate (1.0 equiv.) in CH_2Cl_2 (0.05 M), dichloro(pyridine-2-carboxylato)gold (III) (0.05 equiv) was added in one portion. The mixture was stirred at 50 °C for 30 minutes. The reaction was quenched with triethylamine (0.05 equiv.). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 50:1) to give the corresponding cyclopent-1-enyl acetates.

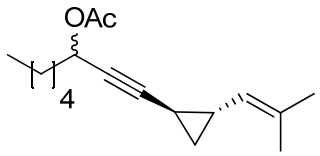
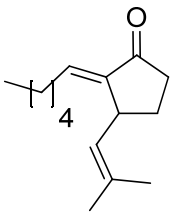
C) To a solution of the corresponding propargyl acetate (1.0 equiv.) in CH_2Cl_2 (0.05 M), $IPrAuNTf_2$ (0.05 equiv.) was added in one portion. The mixture was stirred at room temperature for 30 minutes. The reaction was diluted with methanol and potassium

carbonate (2.0 equiv.) was added. The mixture was stirred at room temperature for 60 minutes. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 25:1) to give the corresponding cyclopentanones.

D) To a solution of the corresponding propargyl acetate (1.0 equiv.) in CH_2Cl_2 (0.05 M), dichloro(pyridine-2-carboxylato)gold (III) (0.05 equiv) was added in one portion. The mixture was stirred at 50 ^oC for 30 minutes. The reaction was diluted with methanol and potassium carbonate (2.0 equiv.) was added. The mixture was stirred at room temperature for 60 minutes. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 25:1) to give the corresponding cyclopentanones.

a. **Complementary Table 2 including methanolysis examples**

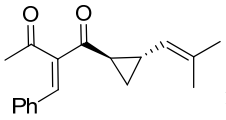
Entry	Substrate	Conditions [a]	Product [b]	Yield (%)[c] (*E*:*Z* ratio) [d]
1	 **5c**	A	 **8c**	81 (14:1)
2	 **5d**	A	 **8d**	78 (10:1)
3	 **5e**	B	 **8e**	78 (12:1)

4		A		60 (50:1)	
	5f		**8f**		

[a] Reaction Conditions A: [(IPr)Au(NTf$_2$)] (5 mol%), CH_2Cl_2, 25 ºC, 30 min. followed by dilution with MeOH and treatment with K_2CO_3 (2 equiv.). B: dichloro(pyridine-2-carboxylato)gold (III) (5 mol%), CH_2Cl_2, 50 ºC, 30 min. followed by dilution with MeOH and treatment with K_2CO_3 (2 equiv.). [b] Only the major product is shown. [c] Isolated yield after column chromatography. [d] Determined by ^{1}H-NMR in the reaction mixture.

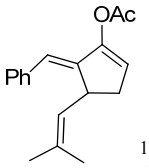
b. Characterization of cyclopent-1-enyl acetates and cyclopentenones

2-Benzylidene-1-(2-(2-methylprop-1-enyl)cyclopropyl)butane-1,3-dione (6b)



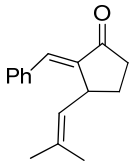
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1H), 7.45-7.35 (m, 5H), 4.50-4.46 (m, 1H), 2.39 (s, 3H), 2.30-2.27 (m, 1H), 1.96-1.91 (m, 1H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.62 (d, *J* = 1.0 Hz, 3H), 1.04-0.99 (m, 2H) ppm; HRMS (ESI): m/z calcd for $C_{18}H_{20}NaO_2^+$: 291.1353, found: 291.1355.

(*E*)-5-Benzylidene-4-(2-metoxyprop-1-enyl)cyclopent-1-enyl acetate (7b)



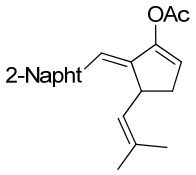
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.35-7.33 (m, 2H), 7.28-7.25 (m, 2H), 7.17-7.14 (m, 1H), 6.33 (s, 1H), 5.92 (t, *J* = 3.0 Hz, 1H), 5.13-5.10 (m, 1H), 4.01 (t, *J* = 7.9 Hz, 1H), 2.96 (ddd, *J* = 17.4, 2.7, 0.6 Hz, 1H), 2.27 (s, 3H), 2.27-2.21 (m, 1H), 1.74 (d, *J* = 1.1 Hz, 3H), 1.62 (d, *J* = 1.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 149.1, 143.5, 136.7, 131.5, 128.6, 127.9, 127.7, 126.3, 119.8, 118.2, 37.8, 36.9, 25.3, 21.1, 18.2 ppm; IR (neat, ν/cm^{-1}): 2926, 1759, 1446, 1369, 1194, 1100, 1077, 1056, 1029, 1012, 802, 755, 693; HRMS (EI): m/z calcd for $C_{18}H_{20}O_2^+$: 268.1463, found: 268.1463.

(*E*)-2-Benzylidene-3-(2-metoxyprop-1-enyl)cyclopentanone (8b)



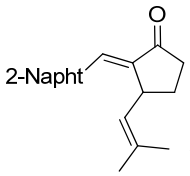
^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.49-7.47 (m, 2H), 7.38-7.32 (m, 4H), 5.15-5.12 (m, 1H), 4.03 (t, *J* = 8.2 Hz, 1H), 2.48-2.40 (m, 1H), 2.35-2.29 (m, 1H), 2.19-2.12 (m, 1H), 1.86-1.80 (m, 1H), 1.84 (s, 3H), 1.68 (s, 3H) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 208.0, 140.9, 135.6, 133.4, 133.2, 131.4, 129.7, 128.8, 126.8, 40.1, 36.8, 29.5, 25.8, 18.5 ppm; IR (neat, ν/cm^{-1}): 2964, 2915, 2872, 2366, 2354, 2340, 1714, 1618, 1448, 1177, 1102, 1026, 806, 754, 693; HRMS (EI): m/z calcd for $C_{16}H_{18}O^+$: 226.1359, found: 226.1358.

(*E*)-4-(2-Methylprop-1-enyl)-5-(naphtalen-1-ylmethylene)cyclopent-1-enyl acetate (7c)



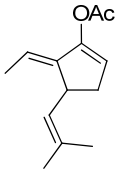
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (s, 1H), 7.77-7.76 (m, 1H), 7.73-7.71 (m, 2H), 7.48-7.39 (m, 3H), 6.49 (s, 1H), 6.00 (t, *J* = 2.8 Hz, 1H), 5.23-5.20 (m, 1H), 4.10 (t, *J* =7.7 Hz, 1H), 3.03-2.97 (m, 1H), 2.32 (s, 3H), 2.31-2.27 (m, 1H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.61 (d, *J* = 1.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 149.2, 144.0, 134.3, 133.5, 132.1, 131.7, 128.0, 127.9, 127.5, 127.4, 127.3, 127.2, 125.9, 125.5, 120.1, 118.2, 38.0, 37.0, 25.4, 21.2, 18.4 ppm; IR (neat, ν/cm^{-1}): 3054, 2968, 2925, 2364, 2354, 2337, 1760, 1613, 1437, 1370, 1199, 1060, 1014, 814, 745; HRMS (ESI): m/z calcd for $C_{22}H_{22}NaO_2^+$: 341.1516, found: 341.1517.

(*E*)-3-(2-Methylprop-1-enyl)-2-(naphtalen-1-ylmethylene)cyclopentanone (8c)



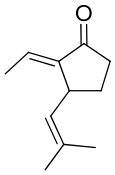
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1H), 7.83-7.77 (m, 3H), 7.59-7.55 (m, 2H), 7.51-7.49 (m, 2H), 5.23-5.20 (m, 1H), 4.15-4.11 (m, 1H), 2.57-2.48 (m, 1H), 2.44-2.37 (m, 1H), 2.28-2.15 (m, 1H), 1.93 (d, *J* = 1.1 Hz, 3H), 1.91-1.84 (m, 1H), 1.71 (d, *J* = 1.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 140.3, 133.5, 133.4, 133.1, 132.8, 132.4, 131.3, 128.5, 127.8, 127.7, 127.6, 127.1, 126.6, 126.4, 39.7, 36.4, 29.0, 25.7, 18.3 ppm; IR (neat, ν/cm^{-1}): 3053, 2963, 2925, 2854, 1710, 1612, 1375, 1259, 1165, 1091, 1016, 798, 744; HRMS (EI): m/z calcd for $C_{20}H_{20}O^+$: 276.1511, found: 276.1514.

(*E*)-5-Ethylidene-4-(2-methylprop-1-enyl)cyclopent-1-enyl acetate (7d)



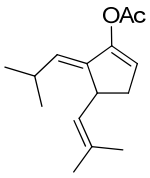
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (t, *J* = 2.7 Hz, 1H), 5.36 (dc, *J* = 7.1, 1.7 Hz, 1H), 5.11-5.09 (m, 1H), 3.66-3.62 (m, 1H), 2.83-2.77 (m, 1H), 2.20 (s, 3H), 2.12-2.08 (m, 1H), 1.70 (dd, *J* = 6.1, 1.4 Hz, 6H), 1.61 (d, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 148.7, 142.3, 129.8, 127.8, 117.8, 113.2, 36.4, 35.5, 25.5, 20.9, 17.9, 13.3; IR (neat, ν/cm^{-1}): 2968, 2914, 2853, 2361, 2333, 1768, 1445, 1370, 1203, 1039, 1019, 829; HRMS (EI): m/z calcd for $C_{13}H_{18}O_2^+$: 296.1306, found 206.1307.

(*E*)-2-Ethylidene-3-(2-methylprop-1-enyl)cyclopentanone (8d)



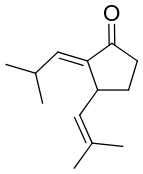
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (dc, *J* = 7.3, 2.5 Hz, 1H), 5.11-5.09 (m, 1H), 3.73-3.67 (m, 1H), 2.44-2.23 (m, 2H), 2.15-2.06 (m, 1H), 1.76 (dd, *J* = 7.3, 1.1 Hz, 3H), 1.74 (s, 3H), 1.71 (s, 3H), 1.67-1.62 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 141.3, 133.2, 131.1, 126.7, 38.2, 37.1, 27.7, 25.6, 17.9, 14.3 ppm; IR (neat, ν/cm^{-1}): 2965, 2927, 2355, 1721, 1645, 1444, 1375, 1214, 1126, 844, 814; HRMS (EI): m/z calcd for $C_{11}H_{16}O^+$: 164.1198, found: 164.1201.

(*E*)-4-(2-Methylprop-1-enyl)-5-(2-methylpropylidene)cyclopent-1-enyl acetate (7e)



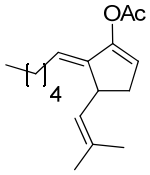
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74 (t, *J* = 2.9 Hz, 1H), 5.14-5.11 (m, 2H), 3.66-3.61 (m, 1H), 2.78 (ddd, *J* = 17.1, 7.9, 2.6 Hz, 1H), 2.49-2.37 (m, 1H), 2.22 (s, 3H), 2.09 (dt, *J* = 17.1, 2.6 Hz, 1H), 1.69 (d, *J* = 1.7 Hz, 3H), 1.68 (d, *J* = 1.7 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 148.3, 139.3, 129.3, 128.6, 126.5, 117.8, 36.2, 35.6, 27.6, 25.5, 23.1, 23.0, 21.1, 17.9 ppm; IR (neat, ν/cm^{-1}): 2963, 2926, 2869, 2359, 1765, 1644, 1447, 1371, 1203, 1146, 1046, 1010, 913, 735; HRMS (ESI): m/z calcd for $C_{15}H_{22}NaO_2^+$: 257.1515, found: 257.1517.

(*E*)-3-(2-Methylprop-1-enyl)-2-(2-methylpropylidene)cyclopentanone (8e)



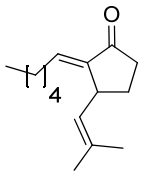
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.39 (dd, *J* = 10.3, 2.5 Hz, 1H), 5.13 (d, *J* = 9.6 Hz, 1H), 3.74-3.68 (m, 1H), 2.60-2.50 (m, 1H), 2.44-2.23 (m, 2H), 2.14-2.05 (m, 1H), 1.73 (s, 3H), 1.71 (s, 3H), 1.67-1.58 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.7, 144.7, 137.9, 130.8, 127.3, 38.2, 37.1, 28.0, 27.8, 25.6, 21.9, 21.9, 17.9; ; IR (neat, ν/cm^{-1}): 2964, 2927, 2868, 1721, 1644, 1455, 1277, 1210, 1176, 983, 940; HRMS (EI): m/z calcd for $C_{13}H_{20}O^+$: 192.1510, found: 192.1514.

(*E*)-5-Hexylidene-4-(2-methylprop-1-enyl)cyclopent-1-enyl acetate (7f)



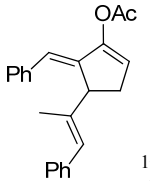
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (t, *J* = 2.9 Hz, 1H), 5.29 (dt, *J* = 7.5, 1.7 Hz, 1H), 5.10 (dt, *J* = 9.9, 1.4 Hz, 1H), 3.62 (t, *J* = 8.8 Hz, 1H), 2.79 (ddd, *J* = 17.1, 7.9, 2.0 Hz, 1H), 2.21 (s, 3H), 2.09 (dt, *J* = 17.1, 2.5 Hz, 1H), 2.05-1.93 (m, 2H), 1.68 (dd, *J* = 4.4, 1.3 Hz, 6H), 1.36-1.22 (m, 6H), 0.88 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 148.6, 141.3, 129.4, 128.3, 119.4, 117.8, 36.4, 35.5, 31.7, 29.5, 28.0, 25.5, 22.5, 21.0, 17.9, 14.0 ppm; IR (neat, ν/cm^{-1}): 2959, 2923, 2854, 1767, 1446, 1369, 1201, 908, 732; HRMS (ESI): m/z calcd for $C_{17}H_{26}NaO_2^+$: 285.1822, found: 285.1825.

(*E*)-2-Hexylidene-3-(2-methylprop-1-enyl)cyclopentanone (8f)



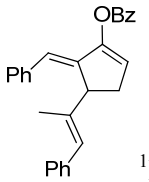
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (dt, *J* = 7.7, 2.6 Hz, 1H), 5.11-5.08 (m, 1H), 3.71-3.66 (m, 1H), 2.43-2.23 (m, 2H), 2.20-2.03 (m, 3H), 1.73 (d, *J* = 1.3 Hz, 3H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.66-1.58 (m, 1H), 1.44-1.36 (m, 2H), 1.31-1.23 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.1, 140.2, 138.7, 130.8, 127.1, 38.3, 37.1, 31.6, 28.5, 28.2, 27.7, 25.6, 22.4, 17.9, 13.9 ppm; IR (neat, ν/cm^{-1}): 2959, 2926, 2857, 1720, 1643, 1455, 1375, 1276, 1215, 1181, 979, 840; HRMS (ESI): m/z calcd for $C_{15}H_{24}NaO^+$: 243.1718, found: 243.1719.

(*E*)-5-Benzylidene-4-((*E*)-1-phenylprop-1-en-2-yl)cyclopent-1-enyl acetate (7g)



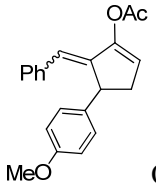
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.39 (d, *J* = 7.4 Hz, 2H), 7.28-7.22 (m, 4H), 7.17-7.13 (m, 2H), 7.03 (d, *J* = 7.4 Hz, 2H), 6.51 (s, 1H), 6.39 (s, 1H), 5.98 (t, *J* = 3.0 Hz, 1H), 3.97-3.96 (m, 1H), 3.01 (ddd, *J* = 17.6, 8.0, 2.9 Hz, 1H), 2.43 (dt, *J* = 17.5, 2.4 Hz, 1H), 2.32 (s, 3H), 1.76 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 150.0, 140.9, 138.4, 138.3, 136.4, 128.8, 128.7, 128.0, 127.9, 126.6, 126.0, 125.9, 119.8, 119.6, 47.7, 35.6, 21.1, 15.2 ppm; IR (neat, ν/cm^{-1}): 3054, 3022, 2913, 1369, 1761, 1493, 1446, 1369, 1195, 1009, 906, 730, 698; MS (ESI) for $C_{23}H_{22}NaO_2^+$ m/z: 353.2 [M^+ + Na].

(*E*)-5-Benzylidene-4-((*E*)-1-phenylprop-1-en-2-yl)cyclopent-1-enyl benzoate (7h)



^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16-8.15 (m, 2H), 7.58-7.55 (m, 1H), 7.47-7.44 (m, 2H), 7.32-7.31 (m, 2H), 7.19-7.15 (m, 4H), 7.08-7.05 (m, 2H), 6.98-6.96 (m, 2H), 6.54 (s, 1H), 6.37 (s, 1H), 6.05 (t, *J* = 2.9 Hz, 1H), 3.96-3.95 (m, 1H), 3.00 (ddd, *J* = 17.6, 8.0, 2.8 Hz, 1H), 2.44-2.40 (m, 1H), 1.72 (d, *J* = 1.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8, 150.2, 141.1, 138.5, 138.3, 136.4, 133.6, 130.1, 129.5, 128.9, 128.8, 128.6, 128.0, 127.9, 126.6, 126.2, 125.9, 120.1, 119.8, 47.8, 35.8, 15.2 ppm; IR (neat, ν/cm^{-1}): 3056, 3022, 2911, 1738, 1598, 1492, 1449, 1261, 1227, 1090, 1021, 906, 727, 699; HRMS (ESI): m/z calcd for $C_{28}H_{24}NaO_2^+$: 415.1666, found: 415.1668.

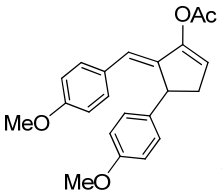
(*E*)-5-Benzylidene-4-(4-methoxyphenyl)cyclopent-1-enyl acetate (7i)



Obtained as a 3:1 mixture of isomers. ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.29-6.96 (m, 7H, major and minor), 6.76-6.73 (m, 2H, minor), 6.72-6.68 (m, 2H, major), 6.41 (s, 1H, major), 6.32 (d, *J* = 1.6 Hz, 1H, minor), 5.83 (t, *J* = 2.8 Hz, 1H, major), 5.18 (m, 1H, minor), 4.27 (d, *J* = 8.0 Hz, 1H, major), 3.84 (m, 1H, minor), 3.67 (s, 3H, minor), 3.66 (s, 3H, major), 3.07 (ddd, *J* = 17.2, 7.7, 2.7 Hz, 1H, major), 2.99 (ddd, *J* = 17.7, 8.3, 2.7 Hz, 1H, minor), 2.42 (ddd, *J* = 12.4, 6.8, 2.0 Hz, 1H, minor), 2.31 (ddd, *J* = 17.2, 3.2, 1.2 Hz, 1H, major), 2.26 (s, 3H, major), 2.13 (s, 3H, minor); ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer) δ = 168.2, 157.9, 150.1, 142.0, 137.1,

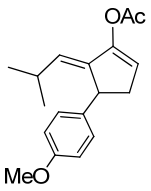
136.3, 128.6, 128.1, 127.9, 126.5, 119.3, 119.2, 114.1, 55.1, 43.5, 39.4, 21.1 ppm; (minor isomer) δ: 169.6, 158.4, 147.0, 140.8, 139.3, 133.5, 128.7, 128.4, 127.6, 125.6, 120.5, 113.9, 108.3, 40.2, 32.0, 29.7, 21.0 ppm; IR (neat, ν/cm^{-1}): 2925, 1757, 1610, 1509, 1246, 1202, 1032, 831; HRMS (EI): m/z calcd for $C_{21}H_{20}O_3^+$: 320.1412, found: 320.1410.

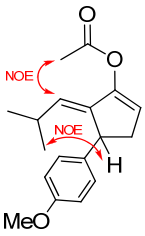
(*E*)-5-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)cyclopent-1-enyl acetate (7j)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.22-7.19 (m, 2H), 7.15-7.12 (m, 2H), 6.81-6.78 (m, 2H), 6.71-6.68 (m, 2H), 6.44 (s, 1H), 5.84 (t, *J* = 2.5 Hz, 1H), 4.32 (d, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.14 (ddd, *J* = 2.5, 8.0, 17.5 Hz, 1H), 2.38 (dd, *J* = 3.0, 17.0 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.2, 158.3, 157.9, 150.2, 139.7, 137.2, 129.9, 129.1, 127.9, 118.7, 118.0, 114.1, 113.6, 55.1, 43.5, 39.3, 21.1; IR (neat, ν/cm^{-1}): 3001, 2932, 2836, 1757, 1606, 1509, 1246, 1201, 1175, 1032, 906, 826; HRMS (ESI): m/z calcd for $C_{22}H_{22}NaO_4^+$: 373.1416, found: 373.1416.

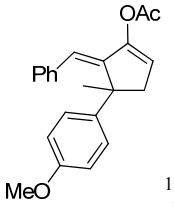
(*E*)-4-(4-Methoxyphenyl)-5-(2-methylpropylidene)cyclopent-1-enyl acetate (7k)





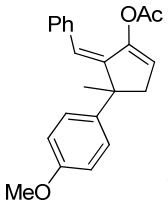
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.16-7.15 (m, 2H), 6.82-6.80 (m, 2H), 5.77 (t, *J* = 2.4 Hz, 1H), 5.20 (dd, *J* = 10, 1.6 Hz, 1H), 3.95 (dt, *J* = 12.0, 2.4 Hz, 1H), 3.78 (s, 3H), 3.03 (ddd, *J* = 17.2, 8.4, 2.8 Hz, 1H), 2.32-2.17 (m, 5H), 0.89 (d, *J* = 17.2 Hz, 3H), 0.52 (d, *J* = 17.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 157.8, 148.9, 139.4, 139.0, 127.9, 127.1, 117.7, 113.8, 55.2, 42.1, 38.6, 27.8, 22.9, 22.3, 21.1; IR (neat, ν/cm^{-1}): 2956, 2924, 2864, 1763, 1509, 1242, 1201, 1039, 829; HRMS (ESI): m/z calcd for $C_{18}H_{22}NaO_3^+$: 309.1467, found: 309.1462.

(*E*)-5-benzylidene-4-(4-methoxyphenyl)-4-methylcyclopent-1-enyl acetate (*E*-7l)



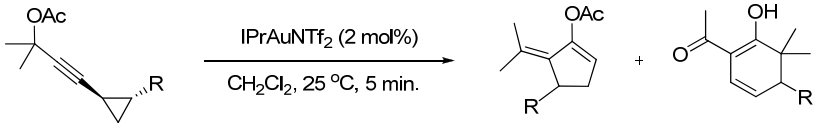
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.48-7.46 (m, 2H), 7.16-7.15 (m, 3H), 7.06-7.04 (m, 2H), 6.87-6.85 (m, 2H), 6.05 (d, *J* = 2.0 Hz, 1H), 5.27 (ddd, *J* = 5.7, 3.5, 2.0 Hz, 1H), 3.79 (s, 3H), 2.74 (dd, *J* = 17.1, 3.6 Hz, 1H), 2.55 (dd, *J* = 17.1, 5.9 Hz, 1H), 2.16 (s, 3H), 1.54 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.5, 158.0, 147.5, 146.5, 140.4, 137.3, 127.8, 127.7, 127.1, 123.1, 113.5, 109.6, 55.1, 42.1, 41.1, 26.9, 20.9 ppm; IR (neat, ν/cm^{-1}): 3056, 2958, 2932, 2834, 1754, 1607, 1509, 1370, 1248, 1213, 1136, 1033, 907, 828, 730, 701; HRMS (ESI): m/z calcd for $C_{22}H_{22}NaO_3^+$: 357.1459, found: 357.1461.

(*Z*)-5-benzylidene-4-(4-methoxyphenyl)-4-methylcyclopent-1-enyl acetate (*Z*-7l)



^{1}H NMR (400MHz, $CDCl_3$) δ = 7.46-7.43 (m, 2H), 7.32-7.27 (m, 5H), 6.88-6.86 (m, 2H), 5.93 (s, 1H), 5.44 (t, *J* = 4.8 Hz, 1H), 3.79 (s, 3H), 2.73 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.56 (dd, *J* = 17.2, 4.8 Hz, 1H), 1.81 (s, 3H), 1.57 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.1, 158.0, 145.3, 139.7, 137.4, 137.3, 134.7, 128.0, 127.9, 127.3, 127.2, 113.5, 112.2, 55.2, 38.8, 38.3, 26.4, 20.4 ppm; IR (neat, ν/cm^{-1}): 3062, 2962, 2828, 2254, 1755, 1608, 1510, 1366, 1249, 1213, 1183, 1143, 1034, 908; HRMS (ESI): m/z calcd for $C_{22}H_{22}NaO_3^+$: 357.1459, found: 357.1461.

2.6 General procedure for the preparation of cyclopent-1-enyl acetates and cyclohexa-1,5-dienylethanones

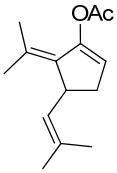


To a solution of the corresponding terciary acetate (1.0 equiv.) in CH_2Cl_2 (0.05 M), $IPrAuNTf_2$ (0.05 equiv.) was added in one portion. The mixture was stirred at room temperature for 5 minutes. The solution was quenched with triethylamine (0.05 equiv.). The solution was filtered through a small path of silica gel and the solvent was evaporated under reduced pressure. The

residue was purified by column chromatography (Hex:AcOEt 50:1) to give a mixture of the corresponding cyclopentenyl acetates and diketones.

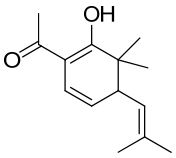
2.5 Characterization of cyclopent-1-enyl acetates and cyclohexa-1,5-dienylethanones

4-(2-Methylprop-1-enyl)-5-(propan-2-ylidene)cyclopent-1-enyl acetate (10a)



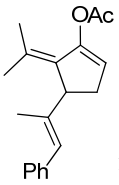
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (m, 1H), 5.16-5.12 (m, 1H), 3.57 (t, *J* = 9.4 Hz, 1H), 2.78-2.70 (m, 1H), 2.19 (s, 3H), 2.02-1.98 (m, 1H), 1.82 (s, 3H), 1.68-1.67 (m, 6H), 1.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 149.8, 134.4, 128.9, 128.8, 123.9, 119.9, 39.2, 34.5, 25.5, 22.6, 21.3, 19.5, 17.9 ppm; IR (neat, ν/cm^{-1}): 2969, 2913, 2854, 2361, 2339, 1767, 1621, 1445, 1369, 1331, 1200, 1056, 1010, 795; HRMS (EI): m/z calcd for $C_{14}H_{20}O_2^+$: 220.1463, found: 220.1463.

1-(2-Hydroxy-3,3-dimethyl-4-(2-methylprop-1-enyl)cyclohexa-1,5-dienyl)ethanone (11a)



^{1}H NMR (400 MHz, CD_2Cl_2): δ = 15.87 (s, 1H), 6.19 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.40 (dd, *J* = 10.0, 5.1 Hz, 1H), 4.93 (dq, *J* = 10.5, 1.3 Hz, 1H), 2.98 (ddd, *J* = 10.5, 5.0, 0.7 Hz, 1H), 2.10 (d, J = 0.6 Hz, 3H), 1.69 (d, *J* = 1.3 Hz, 3H), 1.63 (d, *J* = 1.3 Hz, 3H), 1.14 (s, 3H), 1.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.5, 179.6, 133.7, 123.7, 123.3, 121.3, 107.4, 45.8, 44.8, 26.1, 25.1, 20.4, 19.9, 18.3 ppm; IR (neat, ν/cm^{-1}):3046, 2970, 2928, 2864, 1637, 1592, 1443, 1394, 1257, 1159, 952, 723; HRMS (EI): m/z calcd for $C_{14}H_{20}O_2^+$: 220.1464, found: 220.1463.

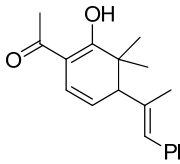
(*E*)-4-(1-Phenylprop-1-en-2-yl)-5-(propan-2-ylidene)cyclopent-1-enyl acetate (10b)



^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.32-7.28 (m, 2H), 7.24-7.22 (m, 2H), 7.18-7.15 (m, 1H), 6.36 (s, 1H), 5.63 (t, *J* = 2.7 Hz, 1H), 3.59 (d, *J* = 8.5 Hz, 1H), 2.84-2.78 (m, 1H), 2.21-2.16 (m, 1H), 2.19 (s, 3H), 1.88 (s, 3H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.71 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 151.4, 141.7, 139.2, 132.9, 129.4, 128.5, 126.4, 126.3, 125.0, 120.6, 50.3, 33.9, 23.2, 21.7, 19.8, 14.8 ppm; IR (neat, ν/cm^{-1}): 3046, 2976, 2363, 1641, 1593, 1444,

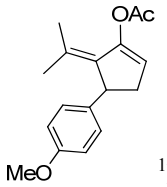
1396, 1354, 1309, 1260, 1162, 1002, 956, 754; HRMS (ESI): m/z calcd for $C_{19}H_{22}NaO_2^+$: 305.1522, found: 305.1517.

(*E*)-1-(2-Hydroxy-3,3-dimethyl-4-(1-phenylprop-1-en-2-yl)cyclohexa-1,5-dienyl)ethanone (11b)[4]



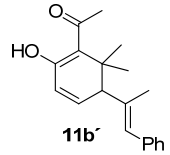
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 15.65 (s, 1H), 7.35-7.31 (m, 2H), 7.24-7.19 (m, 3H), 6.41-6.38 (m, 2H), 5.50 (dd, *J* = 9.7, 6.0 Hz, 1H), 2.91 (d, *J* = 6.0 Hz, 1H), 2.15 (s, 3H), 1.63 (d, *J* = 1.3 Hz, 3H), 1.26 (s, 3H), 1.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5, 178.1, 138.9, 138.6, 129.5, 128.7, 128.6, 126.8, 122.9, 121.2, 107.6, 59.4, 44.4, 28.7, 20.7, 19.5, 14.4 ppm; IR (neat, ν/cm^{-1}): 3051, 3020, 2974, 2932, 2847, 1641, 1592, 1444, 1395, 1309, 1259, 1162, 998, 955, 754, 699; HRMS (ESI): m/z calcd for $C_{19}H_{22}NaO_2^+$: 305.1521, found: 305.1517.

4-(4-Methoxyphenyl)-5-(propan-2-ylidene)cyclopent-1-enyl acetate (10c)

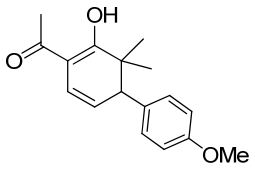


^{1}H NMR (500MHz, $CDCl_3$) δ = 7.21-7.19 (m, 2H), 6.83-6.81 (m, 2H), 5.63 (s, 1H), 3.94 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 2.97 (dd, *J* = 17.0, 8.0 Hz, 1H), 2.24 (s, 3H), 2.17 (d, *J* = 17.0 Hz, 1H), 1.86 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.7, 157.7, 150.5, 139.2, 134.3, 127.8, 125.2, 119.7, 113.8, 55.2, 45.0, 37.2, 23.2, 21.3, 19.3; IR (neat, ν/cm^{-1}): 2911, 2850, 1761, 1509, 1242, 1203, 907; HRMS (ESI): m/z calcd for $C_{17}H_{20}NaO_3^+$: 295.1310, found: 295.1312.

[4] We also studied the possibility of obtaining 1,3 diketones from intermediate **XVIa** (Scheme 9). 2D-NMR experiments confirmed the structure of **11b** ruling out the formation of a regioisomer compound **11b´** (see section 8 in this supporting information).

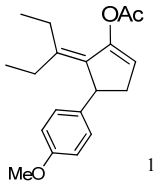


1-(2-Hydroxy-4-(4-methoxyphenyl)-3,3-dimethylcyclohexa-1,5-dienyl)ethanone (11c)



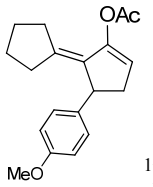
^{1}H NMR (400MHz, $CDCl_3$) δ = 15.82 (s, 1H), 7.06-7.03 (m, 2H), 6.82-6.78 (m, 2H), 6.35 (dd, *J* = 9.6, 1.2 Hz, 1H), 5.65 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.78 (s, 3H), 3.31 (dd, *J* = 14.8, 1.2 Hz, 1H), 2.19 (s, 3H), 1.24 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.6, 178.7, 158.5, 132.7, 129.9, 123.5, 121.4, 113.6, 106.8, 55.2, 52.3, 45.2, 26.2, 20.8, 19.5; IR (neat, ν/cm^{-1}): 2970, 2931, 2835, 1606, 1583, 1509, 1247, 1177, 909; HRMS (EI): m/z calcd for $C_{17}H_{20}NaO_3^+$: 275.1310, found: 275.1310.

4-(4-Methoxyphenyl)-5-(pentan-3-ylidene)cyclopent-1-enyl acetate (10d)



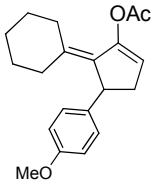
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.21-7.17 (m, 2H), 6.82-6.79 (m, 2H), 5.68 (t, *J* = 2.8 Hz, 1H), 3.93 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 3H), 2.98 (ddd, *J* = 17.2, 8.4, 2.4 Hz, 1H), 2.32-2.15 (m, 6H), 1.91-1.77 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.68 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.6, 157.7, 150.2, 139.9, 137.4, 133.7, 127.7, 119.9, 113.8, 55.2, 44.2, 37.4, 26.9, 23.2, 21.3, 14.2, 12.1; IR (neat, ν/cm^{-1}): 2965, 2933, 2873, 2254, 1757, 1509, 1206, 904, 726; HRMS (EI): m/z calcd for $C_{19}H_{24}O_3^+$: 300.1725, found: 300.1722.

5-Cyclohexylidene-4-(4-methoxyphenyl)cyclopent-1-enyl acetate (10e)



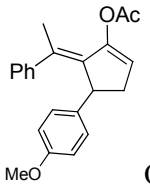
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.20-7.16 (m, 2H), 6.83-6.79 (m, 2H), 6.63 (s, 1H), 3.83 (d, *J* = 8.4 Hz, 1H), 3.78 (s, 3H), 3.02 (dd, *J* = 17.2, 8.4 Hz, 1H), 2.49-2.43 (m, 2H), 2.26 (d, *J* = 17.2 Hz, 1H), 2.23 (s, 3H), 2.10-2.03 (m, 1H), 1.79-1.70 (m, 1H), 1.65-1.52 (m, 2H), 1.50-1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.8, 157.7, 150.4, 138.6, 135.8, 132.1, 128.0, 118.4, 113.8, 55.2, 45.4, 38.1, 32.4, 30.0, 27.1, 25.7, 21.3; IR (neat, ν/cm^{-1}): 2954, 1754, 1509, 1213, 905, 726; HRMS (EI): m/z calcd for $C_{19}H_{22}O_3^+$: 298.1569, found: 298.1569.

5-Cyclohexylidene-4-(4-methoxyphenyl)cyclopent-1-enyl acetate (10f)



^{1}H NMR (400MHz, $CDCl_3$) δ = 7.24-7.20 (m, 2H), 6.84-6.79 (m, 2H), 5.63 (t, *J* = 2.8 Hz, 1H), 3.99 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 2.97 (ddd, *J* = 17.2, 8.0, 2.4 Hz, 1H), 2.51-2.45 (m, 1H), 2.37-2.29 (m, 1H), 2.23 (s, 3H), 2.19-2.14 (m, 1H), 1.95-1.82 (m, 2H), 1.56-1.32 (m, 5H), 1.19-1.07 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.7, 157.6, 150.6, 139.8, 134.2, 130.9, 127.9, 120.6, 113.8, 55.2, 44.5, 37.0, 33.1, 29.3, 28.2, 27.6, 26.5, 21.3; IR (neat, ν/cm^{-1}): 2923, 2850, 1763, 1444, 1243, 1201, 1036, 831; HRMS (EI): m/z calcd for $C_{20}H_{24}O_3^+$: 312.1725 found: 312.1725.

(*E*)-4-(4-Methoxyphenyl)-5-(1-phenylethylidene)cyclopent-1-enyl acetate (10g)



Obtained as a 4:1 mixture of isomers. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.34-7.28 (m, 1H, major), 7.22-7.18 (m, 2H, minor), 7.15-7.13 (m, 3H, minor), 7.12-7.08 (m, 3H, major), 6.89-6.86 (m, 2H, minor), 6.79-6.77 (m, 1H major, 2H minor), 6.75-6.72 (m, 2H, major), 6.62-6.58 (m, 2H, major), 5.87 (t, *J* = 2.4 Hz, 1H, major), 5.61 (t, *J* = 2.0 Hz, 1H, minor), 4.14 (d, *J* = 6.4 Hz, 1H, minor), 3.80 (s, 3H, minor), 3.75 (d, *J* = 6.4 Hz, 1H, major), 3.73 (s, 3H, major), 3.08 (dd, *J* = 13.6, 6.4 Hz, 1H, minor), 3.92 (dd, *J* = 14.0, 6.4 Hz, 1H, major), 2.59-2.57 (m, 1H, minor), 2.29 (s, 3H, major), 2.28-2.16 (m, 1H, minor), 2.13 (s, 3H, major), 1.74 (s, 3H, minor), 1.20 (s, 3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.63, 168.59, 157.87, 157.44, 150.43, 150.05, 144.93, 143.32, 139.72, 138.69, 137.49, 136.09, 130.18, 129.60, 128.56, 127.92, 127.81, 127.71, 127.63, 126.22, 126.02, 122.24, 121.78, 114.05, 113.31, 100.00, 55.23, 55.19, 45.49, 45.00, 37.42, 37.14, 23.48, 21.41, 20.33, 19.61; IR (neat, ν/cm^{-1}): 2933, 2851, 2255, 1756, 1509, 1208, 905, 726; HRMS (EI): m/z calcd. for $C_{22}H_{22}O_3^+$: 334.1569, found: 334.1571.

3 Preparation and characterization of the compounds in Scheme 5

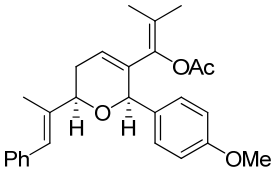
3.1 Procedure for the preparation of compound 12

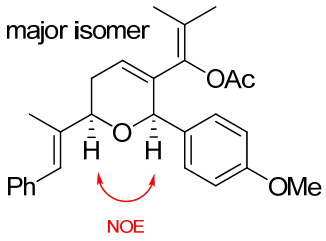
To a solution of **9b** (36.5 mg, 0.129 mmol, 1.0 equiv.) in CH_2Cl_2 (2.5 ml, 0.05 M), *p*-anisaldehyde (18 mg, 0.129 mmol, 1.0 equiv.) and $IPrAuNTf_2$ (5.7 mg, 0.05 equiv.) was added sequentially. The mixture was stirred at room temperature for 30 minutes. The reaction was quenched with

triethylamine (0.05 equiv.). The solution was dried under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 25:1) to give the compounds **10b**, **11b** and compound **12** (4.6 mg, 0.011 mmol) in 9% yield.

3.2 Characterization of compound 12

(*E*)-1-(6-(4-Methoxyphenyl)-4-(1-phenylprop-1-en-2-yl)cyclohex-1-enyl)-2-methylprop-1-enyl acetate (12) (some carbon signals are missing due to overlapping)





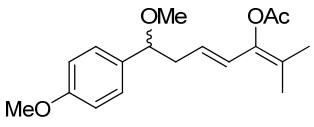
Obtained as a 2:1 mixture of diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 6H, major and minor), 7.24-7.21 (m, 1H, major and minor), 6.88-6.84 (m, 2H, major and minor), 6.74 (s, 1H, minor), 6.70 (s, 1H, major), 5.13 (d, *J* = 8.0 Hz, 1H, minor), 5.01 (d, *J* = 7.1 Hz, 1H, major), 4.51-4.64 (m, 1H, major and minor), 3.80 (s, 3H, major), 3.79 (s, 3H, minor), 3.43-3.35 (m, 1H, major and minor), 2.57-2.52 (m, 1H, major), 2.37-2.32 (m, 1H, minor), 2.10-2.04 (m, 1H, major), 2.00 (d, *J* = 1.1 Hz, 3H, major), 1.96 (d, *J* = 1.1 Hz, 3H, minor), 1.92-1.82 (m, 1H, minor), 1.91 (s, 3H, minor), 1.90 (s, 3H, major), 1.68 (s, 3H, minor), 1.55 (m, 3H, minor), 1.37 (s, 3H, major), 1.34 (s, 3H, major) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major and minor isomer): 192.4, 169.2, 168.2, 159.0, 158.9, 137.8, 137.7, 137.1, 137.0, 132.4, 131.9, 129.1, 128.3, 128.2, 128.1, 126.4, 126.3, 125.0, 119.6, 113.1, 113.0, 109.3, 85.7, 84.1, 83.7, 83.1, 82.7, 82.6, 72.1, 55.3, 55.2, 46.9, 38.5, 36.9, 34.9, 28.8, 21.9, 21.4, 21.2, 21.1, 14.4, 13.9 ppm; IR (neat, ν/cm^{-1}): 2982, 2937, 2828, 2253, 1974, 1742, 1614, 1513, 1364, 1245, 1134, 1036, 909, 730, 700; HRMS (ESI): m/z calcd for $C_{27}H_{30}NaO_4^+$: 441.2035, found: 441.2036.

3.3 Procedure for the preparation of compound 13

To a solution of **9c** (41 mg, 0.15 mmol, 1.0 equiv.) in a mixture 10:1 CH_2Cl_2:methanol (2.2 ml, 0.05 M), $IPrAuNTf_2$ (6.5 mg, 0.05 equiv.) was added in one portion. The mixture was stirred at room temperature for 30 minutes. The reaction was quenched with triethylamine (0.05 equiv.). The solution was dried under reduced pressure and the residue was purified by column chromatography (Hex:EtOAc 25:1) to give the compound **13** (13 mg, 0.043 mmol) in 28% of yield.

3.4 Characterization of compound 13

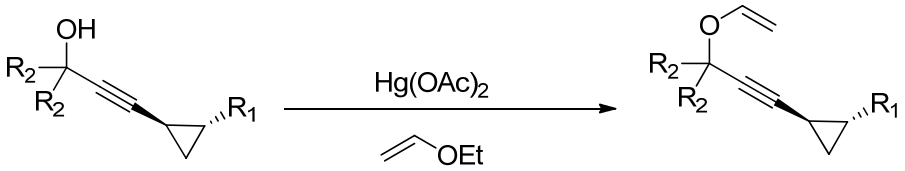
(*E*)-7-Methoxy-7-(4-methoxyphenyl)-2-methylhepta-2,4-dien-3yl acetate (13)



Obtained as a mixture 1:1 of isomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.20-7.17 (m, 4H), 6.90-6.87 (m, 4H), 6.26 (d, *J* = 15.5 Hz, 2H), 5.44 (t, *J* = 7.6 Hz, 1H), 5.41 (t, *J* = 7.6 Hz, 1H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.81 (s, 6H), 3.18 (s, 6H), 2.63-2.57 (m, 2H), 2.44-2.38 (m, 2H), 2.16 (s, 6H), 1.80 (s, 6H), 1.61 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.9, 159.1, 140.3, 133.6, 127.9, 125.1, 122.9, 122.3, 113.8, 83.4, 56.5, 55.3, 41.3, 20.5, 18.5, 18.4; IR (neat, ν/cm^{-1}): 2934, 2836, 1753, 1610, 1510, 1245, 1209, 1175, 1098, 1034, 910, 831, 729; HRMS (EI): m/z calcd for $C_{18}H_{24}NaO_4^+$: 327.1572, found: 327.1575.

4 Preparation and characterization of 3-cyclopropyl propargyl vinyl ethers and cyclization products

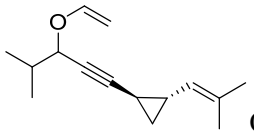
4.1 General procedure for the preparation of secondary and tertiary propargyl vinyl ethers[5]



To a solution of the corresponding propargyl alcohol (1.0 equiv.) in ethyl vinyl ether (0.4 M), mercury (II) acetate (0.67 equiv.) was added in one portion. The mixture was stirred at room temperature for 12-24 hours. The reaction was poured into 5% potassium hydroxide solution and extracted several times with hexane. The organic layers were dried over Na_2SO_4. The solvent was dried under reduced pressure. The residue was purified by column chromatography (Hexane) to give the corresponding propargyl vinyl ethers in 29-84% yield.

4.2 Characterization of secondary propargyl vinyl ethers[3]

1-(4-Methyl-3-(vynyloxy)pent-1-ynyl)-2-(2-methylprop-1enyl)cyclopropane (16a)

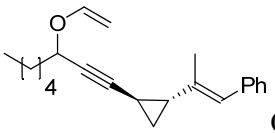


Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.42 (dd, *J* = 14.1, 6.5 Hz, 2H), 4.55-4.53 (m, 2H), 4.37 (dd, *J* = 14.1, 1.6

[5] K. Nososhita, H. Banno, K. Maruoka, H. Yamamoto; *J. Am. Chem. Soc.* **1990**, *112*, 316-322.

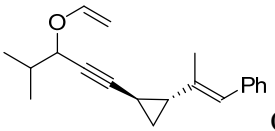
Hz, 2H), 4.16 (d, *J* = 5.8 Hz, 1H), 4.15 (d, *J* = 5.8 Hz, 1H), 4.07 (dd, *J* = 6.6, 1.6 Hz, 2H), 1.99-1.91 (m, 2H), 1.79-1.72 (m, 2H), 1.75 (s, 6H), 1.67 (d, *J* = 1.3 Hz, 6H), 1.21-1.15 (m, 2H), 1.06-0.96 (m, 2H), 1.00 (d, *J* = 6.7 Hz, 6H), 0.96 (d, *J* = 6.7 Hz, 6H), 0.77-0.73 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2 (2xC), 133.4 (2xC), 125.3 (2xC), 89.8 (2xC), 89.0, 74.8 (2xC), 73.0, 33.1, 25.4, 21.7, 21.6, 18.3 (2xC), 17.7, 16.7 (2xC), 8.5 ppm; IR (neat, ν/cm^{-1}): 2963, 2927, 2873, 2230, 1634, 1614, 1468, 1385, 1188, 1132, 1047, 1003, 908, 816, 732; HRMS (EI): m/z calcd for $C_{15}H_{22}O^+$: 218.1669, found: 218.1671.

(*E*)-1-(2-(2-(3-(Vinyloxy)oct-1-ynyl)cyclopropyl)prop-1-enyl)benzene (16b)



Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.29 (m, 4H), 7.22-7.17 (m, 6H), 6.44 (dd, *J* = 14.2, 6.6 Hz, 2H), 6.34 (s, 2H), 4.41 (dd, *J* = 14.2, 1.5 Hz, 2H), 4.40 (t, *J* = 6.6 Hz, 1H), 4.39 (t, *J* = 6.6 Hz, 1H), 4.11 (dd, *J* = 6.7, 1.5 Hz, 2H), 1.92-1.84 (m, 2H), 1.79-1.71 (m, 2H), 1.74 (d, *J* = 1.3 Hz, 6H), 1.50-1.42 (m, 6H), 1.38-1.26 (m, 10H), 1.16-1.11 (m, 2H), 1.08-1.02 (m, 2H), 0.91 (t, *J* = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 137.9, 136.4, 129.3, 128.8, 128.1, 126.1, 125.1, 89.2 (2xC), 74.4, 69.4, 35.6, 31.4, 30.8 (2xC), 24.8, 22.5, 15.6, 14.7, 13.9, 7.2 ppm; IR (neat, ν/cm^{-1}): 3015, 2929, 2859, 2232, 1635, 1614, 1444, 1339, 1186, 1041, 909, 818, 733, 698; HRMS (ESI): m/z calcd for $C_{22}H_{28}NaO^+$: 331.2032, found: 331.2032.

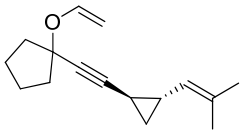
(*E*)-1-(2-(2-(4-Methyl-3-(vinyloxy)pent-1-ynyl)cyclopropyl)prop-1-enyl)benzene (16c)



Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.29 (m, 4H), 7.22-7.17 (m, 6H), 6.44 (dd, *J* = 13.9, 6.4 Hz, 2H), 6.34 (s, 2H), 4.40 (dd, *J* = 13.9, 1.5 Hz, 2H), 4.19 (d, *J* = 5.8 Hz, 1H), 4.18 (d, *J* = 5.8 Hz, 1H), 4.10 (dd, *J* = 6.4, 1.5 Hz, 2H), 2.04-1.94 (m, 2H), 1.92-1.86 (m, 2H), 1.75 (d, *J* = 1.3 Hz, 6H), 1.50-1.43 (m, 2H), 1.17-1.11 (m, 2H), 1.08-1.02 (m, 2H), 1.02 (d, *J* = 6.8 Hz, 6H), 1.00 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 137.9, 136.5, 128.8, 128.1, 126.1, 125.1, 89.8, 89.1, 74.8, 73.0, 33.1, 30 8 (2xC), 18.4, 17.7, 15.6, 14.8 (2xC), 7.2 ppm; IR (neat, ν/cm^{-1}): 3020, 2963, 2926, 2829, 2354, 1635, 1608, 1467, 1447, 1187, 1048, 912, 818, 736, 699; HRMS (EI): m/z calcd for $C_{20}H_{24}O^+$: 280.1830, found: 280.1827.

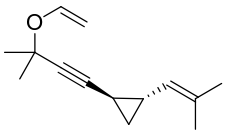
4.3 Characterization of tertiary propargyl vinyl ethers

1-(2-(2-(2-Methylprop-1-enyl)cyclopropyl)ethynyl)1-(vinyloxy)cyclopentane (16f)



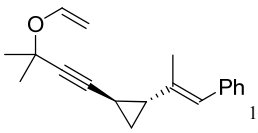
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (dd, *J* = 13.9, 6.3 Hz, 1H), 4.55-4.52 (m, 1H), 4.42 (d, *J* = 14.0 Hz, 1H), 4.10 (d, *J* = 6.4 Hz, 1H), 2.07-2.01 (m, 2H), 1.88-1.79 (m, 2H), 1.78-1.68 (m, 5H), 1.75 (s, 3H), 1.67 (s, 3H), 1.19-1.14 (m, 1H), 1.04-1.00 (m, 1H), 0.74 (ddd, *J* = 8.5, 5.8, 4.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 133.3, 125.3, 91.3, 88.3, 82.0, 76.9, 40.23, 40.22, 25.4, 23.4, 23.4, 21.6, 18.4, 16.7, 8.5 ppm; IR (neat, ν/cm^{-1}): 2965, 2874, 2234, 1632, 1439, 1375, 1306, 1166, 1011, 946, 910, 831, 731; HRMS (EI): m/z calcd for $C_{16}H_{22}O^+$: 230.1668, found: 230.1671.

1-(3-Methyl-3-(vinyloxy)but-1-ynyl)-2-(2-methylprop-1-enyl)cyclopropane (16g)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (dd, *J* = 13.8, 6.3 Hz, 1H, minor), 6.64 (dd, *J* = 13.8, 6.3 Hz, 1H, major), 4.95-4.93 (m, 1H, minor), 4.55-4.53 (m, 1H, major), 4.44 (d, *J* = 13.8 Hz, 1H, major and minor), 4.10 (d, *J* = 6.3 Hz, 1H, major), 4.09 (d, *J* = 6.3 Hz, 1H, minor), 1.78-1.67 (m, 1H, major), 1.75 (s, 3H, major), 1.74 (s, 3H, major), 1.68 (s, 6H, minor), 1.58-1.50 (m, 1H, minor), 1.49 (s, 3H, minor), 1.48 (s, 3H, minor), 1.47 (s, 6H, major) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer): δ = 147.4, 133.4, 125.3, 90.9, 87.9, 77.6, 72.5, 29.5 (2xC), 25.4, 21.6, 18.4, 16.7, 8.4; (minor isomer): 147.5, 134.0, 123.1, 90.8, 86.3, 79.7, 72.5, 29.5, 29.4, 25.7, 18.4, 17.3, 16.1, 7.0 ppm; IR (neat, ν/cm^{-1}): 2984, 2931, 2361, 2237, 1632, 1442, 1378, 1362, 1262, 1200, 1133, 1011, 949, 835; HRMS (ESI): m/z calcd for $C_{14}H_{20}NaO^+$: 227.1410, found: 227.1412.

(*E*)-1-(2-(2-(3-Methyl-3-(vinyloxy)but-1-ynyl)cyclopropyl)prop-1-enyl)benzene (16h)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.30 (m, 2H), 7.22-7.18 (m, 3H), 6.67 (dd, *J* = 14.0, 6.3 Hz, 1H), 6.35 (s, 1H), 4.47 (d, *J* = 14.0 Hz, 1H), 4.13 (d, *J* = 6.3 Hz, 1H), 1.91-1.86 (m, 1H), 1.75 (s, 3H), 1.50 (s, 6H), 1.48-1.43 (m, 1H), 1.17-1.12 (m, 1H), 1.07-1.02 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 137.9, 136.4, 128.8, 128.1, 126.1, 125.2, 91.1, 87.9, 77.5, 72.4, 30.8, 29.5, 29.5, 15.6, 14.7, 7.0 ppm; IR (neat, ν/cm^{-1}): 3022, 2984, 2934, 2235,

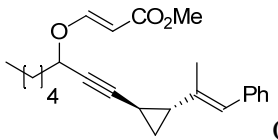
1632, 1493, 1440, 1362, 1261, 1200, 1138, 1123, 1010, 910, 827, 798, 732, 697; HRMS (EI): m/z calcd for $C_{19}H_{22}O^+$: 266.1668, found: 266.1671.

4.4 General procedure for the preparation of acrylates 16d and 16e

To a solution of the corresponding propargyl alcohol (1.0 equiv.) in THF (0.15 M), NMM (4.0 equiv.) and methylpropiolate (2.0 equiv.) were added sequentially. The mixture was stirred for 12 hours. The reaction was quenched with water and extracted with diethyl ether. The organic layers were dried over Na_2SO_4. The residue was purified by column chromatography (Hex:AcOEt 8:1) to give the corresponding 2-(2-methylenecyclopentylidene)-3-oxopropanoates.

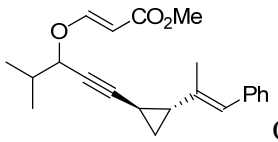
4.5 Characterization of the acrylates 16d and 16e

(*E*)-Methyl 3-(1-(2-((*E*)-1-pnehylprop-1-en-2-yl)cyclopropyl)oct-1-yn-3-yloxy)acrylate (16d)



Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 12.5 Hz, 2H), 7.32-7.29 (m, 4H), 7.21-7.17 (m, 6H), 6.34 (s, 2H), 5.37 (d, *J* = 12.5 Hz, 2H), 4.54 (t, *J* = 6.5 Hz, 1H), 4.53 (t, *J* = 6.5 Hz, 1H), 3.71 (s, 6H), 1.93-1.88 (m, 2H), 1.84-1.77 (m, 2H), 1.75 (d, *J* = 1.3 Hz, 6H), 1.48-1.41 (m, 6H), 1.36-1.26 (m, 10H), 1.18-1.14 (m, 2H), 1.08-1.04 (m, 2H), 0.92-0.88 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 160.8, 137.8, 136.1, 128.8, 128.1, 126.1, 125.3, 98.1, 90.9, 72.9, 72.3, 51.1, 35.6, 31.2, 30.9 (2xC), 24.6, 22.4, 15.6, 14.7, 13.9, 7.08 ppm; IR (neat, ν/cm^{-1}): 2952, 2926, 2859, 2232, 1714, 1643, 1622, 1435, 1328, 1284, 1188, 1132, 954, 915, 831, 739, 699; HRMS (ESI): m/z calcd for $C_{24}H_{30}NaO_3^+$: 389.2091, found: 389.2087.

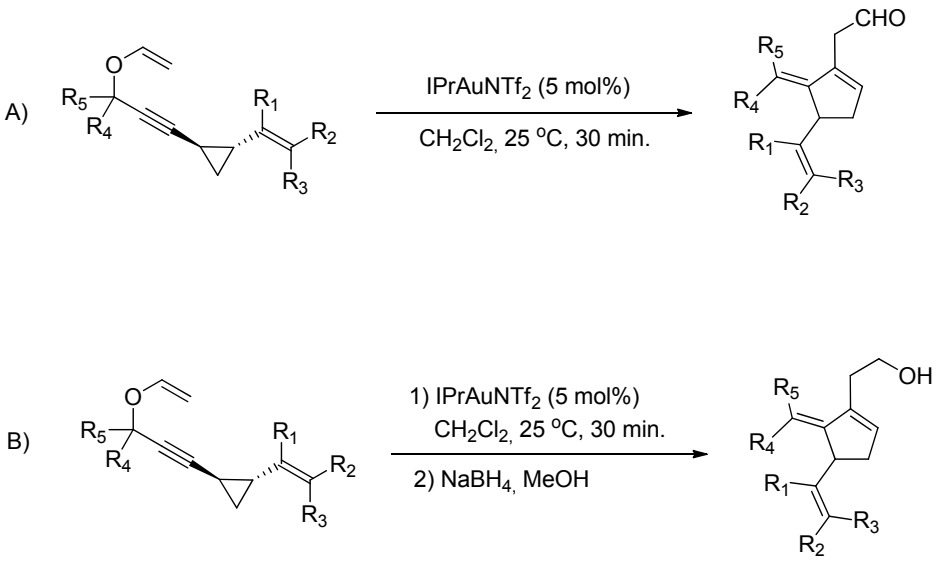
(*E*)-Methyl-3-(4-methyl-1-(2-((*E*)-1-phenylprop-1-en-2-yl)cyclopropyl)pent-1-yn-3-yloxy)acrylate (16e)



Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 12.5 Hz, 2H), 7.33-7.30 (m, 4H), 7.22-7.17 (m, 6H), 6.34 (s, 2H), 5.37 (d, *J* = 12.5 Hz, 2H), 4.33 (d, *J* = 5.7 Hz, 1H), 4.32 (d, *J* = 5.7 Hz, 1H), 3.71 (s, 6H), 2.05-1.99 (m, 2H), 1.93-1.88 (m, 2H), 1.75 (d, *J* = 1.2 Hz, 6H), 1.49-1.45 (m, 2H), 1.18-1.14 (m, 2H), 1.09-1.04 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 6H), 1.00 (d, *J* = 6.7 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 161.1, 137.8, 136.2, 128.8, 128.1, 126.1, 125.3, 97.9, 91.7, 77.6,

71.5, 51.0, 33.2, 30.9 (2xC), 18.1, 17.6, 15.6, 14.8 (2xC), 7.1 ppm; IR (neat, ν/cm^{-1}): 3082, 2964, 2874, 2233, 1713, 1643, 1622, 1435, 1327, 1284, 1192, 1123, 983, 833, 740, 699; HRMS (ESI): m/z calcd for $C_{22}H_{26}O_3Na^+$: 361.1777, found: 361.1774.

4.5 General procedure for the cyclization of 3-cyclopropyl propargylic vinyl ethers

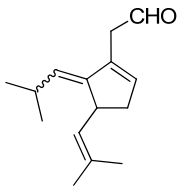


A) To a solution of the corresponding 3-cyclopropyl propargyl enol ether (1.0 equiv.) in CH_2Cl_2 (0.05 M), $IPrAuNTf_2$ (0.05 equiv.) was added in one portion. The mixture was stirred at room temperature for 30 minutes. The reaction was quenched with triethylamine (0.05 equiv.). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 25:1) to give the corresponding acetaldehyde.

B) To a solution of the corresponding 3-cyclopropyl propargyl enol ether (1.0 equiv.) in CH_2Cl_2 (0.05 M), $IPrAuNTf_2$ (0.05 equiv.) was added in one portion. The mixture was stirred at room temperature for 30 minutes. The reaction was diluted with MeOH and $NaBH_4$ (1.0 equiv) was added in one portion. The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (Hex:AcOEt 10:1) to give the corresponding alcohol.

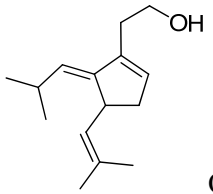
4.6 Characterization of cyclization products from 3-cyclopropyl propargylic vinyl ethers

2-(4-(2-Methylprop-1-enyl)-5-(2-methylpropylidene)cyclopent-1-enyl)acetaldehyde (17a)



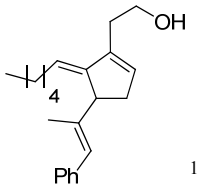
Obtained as a 1:1 mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (t, *J* = 2.5 Hz, 1H, minor), 9.59 (t, *J* = 2.5 Hz, 1H, major), 5.87 (s, 1H, major), 5.51(s, 1H, minor), 5.47-5.45 (m, 1H, minor), 5.20-5.17 (m, 1H, minor), 5.06-4.97 (m, 2H, major), 3.72-3.67 (m, 1H, major and minor), 3.16 (s, 2H, major), 3.08 (s, 2H, minor), 2.99-2.94 (m, 1H, minor), 2.83-2.76 (m,1H, major), 2.48-2.39 (m, 1H, major), 2.27-2.19 (m, 1H, minor), 2.14-2.09 (m, 1H, major and minor), 1.69 (s, 3H, major), 1.67 (s, 3H, major), 1.66-1.65 (m, 6H, minor), 1.03 (t, *J* = 6.8 Hz, 6H, minor), 0.94 (d, *J* = 6.5 Hz, 3H, major), 0.90 (d, *J* = 6.5 Hz, 3H, major) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer): δ = 220.1, 146.7, 135.1, 134.4, 129.1, 129.0, 127.9, 42.3, 39.2, 38.7, 28.1, 25.5, 23.2, 23.1, 17.9 ppm, (minor isomer): 200.6, 151.6, 131.2, 127.1, 126.2, 121.6, 117.5, 50.36, 34.2, 32.7, 31.6, 30.9, 25.8, 22.5, 21.2 ppm; IR (neat, ν/cm^{-1}): 2964, 2925, 2865, 2718, 1726, 1445, 1376, 1038, 908, 852, 731; HRMS (EI): m/z calcd for $C_{15}H_{22}O^{+}$: 218.1667, found: 218.1671.

2-(4-(2-Methylprop-1-enyl)-5-(2-methylpropylidene)cyclopent-1-enyl)ethanol (18a)



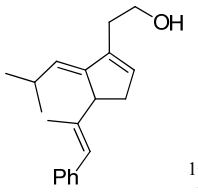
Obtained as a 2:1 mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (s, 1H, major), 5.56 (s, 1H, minor), 5.39-5.37 (m, 1H, minor), 5.17-5.14 (m, 1H, minor), 5.07 (dd, *J* = 9.7, 1.8 Hz, 1H, major), 5.05-5.02 (m, 1H, major), 3.76 (t, *J* = 6.4 Hz, 2H, major and minor), 3.72-3.63 (m, 2H, major and minor), 2.97-2.92 (m, 1H, minor), 2.77-2.70 (m, 1H, major), 2.47-2.39 (m, 3H, major and minor), 2.31 (t, *J* = 6.5 Hz, 1H, major), 2.24-2.21 (m, 1H, minor), 2.07-2.03 (m, 1H, major and minor), 1.69-1.65 (m, 6H, major and minor), 1.43 (br, 1H, major and minor), 1.03 (dd, *J* = 10.6, 6.8 Hz, 6H, minor), 0.93 (dd, *J* = 16.9, 6.6 Hz, 6H, major) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer): δ = 146.7, 140.2, 131.5, 129.5, 128.6, 126.9, 61.1, 38.9, 38.8, 30.6, 28.0, 25.5, 23.3, 23.2, 17.9 ppm, (minor isomer): δ = 151.1, 132.1, 131.0, 126.6, 119.1, 117.5, 60.9, 38.9, 38.8, 34.4, 32.7, 30.8, 25.8, 22.5, 21.3 ppm; HRMS (EI): m/z calcd for $C_{15}H_{24}O^{+}$: 220.1825, found: 220.1827.

2-((*E*)-5-Hexylidene-4-((*E*)-1-phenylprop-1-en-2-yl)cyclopent-1-enyl)ethanol (18b)



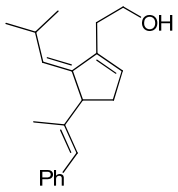
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.32-7.28 (m, 2H), 7.22-7.15 (m, 3H), 6.25 (s, 1H), 5.79 (s, 1H), 5.39-5.37 (m, 1H), 3.68-3.58 (m, 2H), 2.87 (dd, *J* = 9.8, 4.1 Hz, 1H), 2.56-2.34 (m, 2H), 2.28 (t, *J* = 6.4 Hz, 2H), 2.07 (t, *J* = 7.7 Hz, 2H), 1.85 (d, *J* = 1.3 Hz, 3H), 1.59-1.43 (m, 3H), 1.37-1.27 (m, 4H), 0.92-0.88 (m, 3H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 142.7, 139.2, 138.9, 132.7, 129.4, 128.5, 126.4, 125.4, 123.0, 119.7, 61.3, 46.4, 39.5, 36.0, 32.3, 29.3, 28.5, 23.2, 16.7, 14.4 ppm; IR (neat, ν/cm^{-1}): 3332, 2952, 2924, 2854, 1598, 1493, 1446, 1045, 916, 858, 746, 699; HRMS (ESI): m/z calcd for $C_{22}H_{30}NaO^+$: 333.2186, found: 333.2189.

2-((*E*)-5-(2-Methylpropylidene)-4-((*E*)-1-phenylprop-1-en-2-yl)cyclopent-1-enyl)ethanol (18c, major isomer)



^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.32-7.28 (m, 2H), 7.25-7.15 (m, 3H), 6.36 (s, 1H), 5.79 (s, 1H), 5.26-5.23 (m, 1H), 3.77-3.69 (m, 3H), 2.84-2.77 (m, 1H), 2.74-2.65 (m, 1H), 2.45-2.42 (m, 2H), 2.27-2.21 (m, 1H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.27 (m,1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 144.9, 142.3, 142.2, 139.2, 132.1, 129.3, 128.6, 128.5, 126.4, 125.0, 61.5, 50.2, 38.4, 31.2, 28.4, 23.5, 23.3, 14.2 ppm; IR (neat, ν/cm^{-1}): 3370, 3025, 2957, 2921, 2869, 2025, 1733, 1488, 1444, 1379, 1358, 1044, 743, 699; HRMS (ESI): m/z calcd for $C_{20}H_{26}NaO^+$: 305.1873, found: 305.1876.

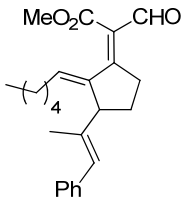
2-((*Z*)-5-(2-Methylpropylidene)-4-((*E*)-1-phenylprop-1-en-2-yl)cyclopent-1-enyl)ethanol (18c, minor isomer)



^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.33-7.29 (m, 2H), 7.22-7.16 (m, 3H), 6.26 (s, 1H), 5.85 (s, 1H), 5.39-5.36 (m, 1H), 3.69-3.62 (m, 2H), 2.92 (dd, *J* = 9.5, 2.9 Hz, 1H), 2.58-2.51 (m, 1H), 2.44-2.38 (m, 1H), 2.35-2.26 (m, 3H), 1.87 (d, *J* = 1.3 Hz, 3H), 1.44-1.42 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 148.5, 139.2, 138.7, 132.8, 129.4, 128.5, 126.4, 125.3, 120.9, 119.8, 61.3, 45.1, 39.6, 33.8, 29.6, 23.2,

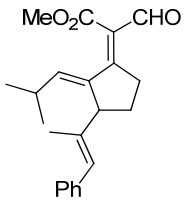
21.8, 17.0 ppm; IR (neat, ν/cm^{-1}): 3370, 3025, 2957, 2921, 2869, 2025, 1733, 1488, 1444, 1379, 1358, 1044, 743, 699; HRMS (ESI): m/z calcd for $C_{20}H_{26}NaO^{+}$: 305.1873, found: 305.1875.

(*Z*)-Methyl 2-((*E*)-2-hexylidene-3-((*E*)-1-phenylprop-1-en-2-yl)cyclopentylidene)-3-oxopropanoate (17d)



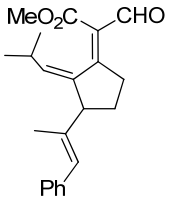
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.10 (s, 1H), 7.34-7.31 (m, 3H), 7.25-7.18 (m, 3H), 6.24 (s, 1H), 3.79 (s, 3H), 3.11 (t, *J* = 5.4 Hz, 1H), 2.74-2.51 (m, 2H), 2.26-2.21 (m, 2H), 1.97-1.90 (m, 2H), 1.86 (d, *J* = 1.1 Hz, 3H), 1.63-1.47 (m, 2H), 1.36-1.30 (m, 4H), 0.91-0.88 (m, 3H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 188.4, 167.9, 161.0, 157.5, 138.5, 138.2, 129.4, 128.6, 128.2, 126.9, 126.7, 121.6, 52.4, 49.3, 37.7, 32.2, 28.3, 27.3, 26.9, 23.1, 17.6, 14.3 ppm; IR (neat, ν/cm^{-1}): 2952, 2928, 2857, 1731, 1681, 1660, 1609, 1539, 1433, 1130, 750, 700; HRMS (ESI): m/z calcd for $C_{24}H_{30}NaO_3^{+}$: 389.2083, found: 389.2087.

(*Z*)-Methyl 2-((*E*)-2-(2-methylpropylidene)-3-((*E*)-1-1phenylprop-1-en-2-yl)cyclopent ylidene)-3-oxopropanoate (17e)



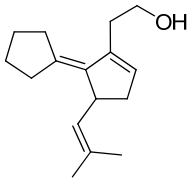
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.00 (s, 1H), 7.34-7.30 (m, 2H), 7.23-7.18 (m, 3H), 6.63 (s, 1H), 6.19 (s, 1H), 3.83 (s, 3H), 3.18 (t, *J* = 4.7 Hz, 1H), 3.05-2.99 (m, 1H), 2.90-2.81 (m, 1H), 2.46 (sept, *J* = 6.7 Hz, 1H), 2.02-1.89 (m, 2H), 1.90 (d, *J* = 1.3 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 167.7, 166.6, 156.9, 138.6, 137.9, 129.4, 128.6, 128.2, 127.9, 126.9, 122.3, 52.5, 48.0, 35.2, 27.2, 23.1, 22.9, 21.3, 18.2 ppm; IR (neat, ν/cm^{-1}): 2959, 2926, 2869, 1733, 1661, 1608, 1539, 1433, 1330, 1240, 1139, 743, 701; HRMS (ESI): m/z calcd for $C_{22}H_{26}NaO_3^{+}$: 361.1775, found: 361.1774.

(*Z*)-Methyl 2-((*E*)-2-(2-methylpropylidene)-3-((*E*)-1-1phenylprop-1-en-2-yl)cyclopent ylidene)-3-oxopropanoate (17e)



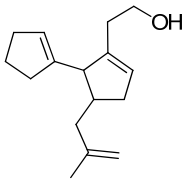
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.12 (s, 1H), 7.40 (s, 1H), 7.34-7.30 (m, 2H), 7.26-7.18 (m, 3H), 6.20 (s, 1H), 3.78 (s, 3H), 3.17 (t, *J* = 4.9 Hz, 1H), 2.74-2.65 (m, 1H), 2.60-2.53 (m, 1H), 2.48 (sept, *J* = 7.0 Hz, 1H), 1.97-1.90 (m, 2H), 1.89 (t, *J* = 1.3 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 188.4, 167.9, 166.4, 157.6, 138.6, 129.4, 128.6, 128.2, 126.9, 126.8, 119.2, 52.4, 48.3, 35.2, 27.3, 26.4, 23.1, 21.4, 18.0 ppm; IR (neat, ν/cm^{-1}): 2959, 2926, 2869, 1733, 1661, 1608, 1539, 1433, 1330, 1240, 1139, 743, 701; HRMS (ESI): m/z calcd for $C_{22}H_{26}NaO_3^+$: 361.1775, found: 361.1774.

2-(5-Cyclopentylidene-4-(2-methylprop-1-enyl)cyclopent-1-enyl)ethanol (18f)



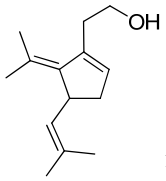
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.67 (s, 1H), 4.98-4.94 (m, 1H), 3.72-3.71 (m, 2H), 3.53-3.49 (m, 1H), 2.73-2.53 (m, 3H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.32-2.11 (m, 2H), 1.95 (d, *J* = 17.1 Hz, 1H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.64-1.55 (m, 4H), 1.48-1.46 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 141.5, 139.9, 134.4, 132.3, 129.2, 129.1, 62.2, 43.1, 39.0, 34.0, 33.3, 31.5, 28.2, 26.5, 25.8, 18.2 ppm; IR (neat, ν/cm^{-1}): 3322, 2950, 2932, 2864, 1733, 1447, 1374, 1043, 957, 802; HRMS (EI): m/z calcd for $C_{16}H_{24}O^+$: 232.1825, found: 232.1827.

2-(5-Cyclopentenyl-4-(2-methylallyl)cyclopent-1-enyl)ethanol (18f')



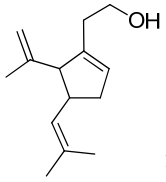
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.69 (s, 1H), 5.63-5.62 (m, 1H), 4.79-4.77 (m, 2H), 3.67-3.62 (m, 2H), 3.55-3.51 (m, 1H), 3.04-3.02 (m, 1H), 2.74-2.09 (m, 9H), 1.97 (d, *J* = 17.1 Hz, 1H), 1.75-1.55 (m, 6H), 1.48-1.44 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 148.3, 148.1, 142.1, 126.7, 115.9, 112.0, 63.7, 61.9, 39.9, 39.8, 39.2, 36.4, 32.1, 27.5, 26.6, 19.3 ppm; IR (neat, ν/cm^{-1}): 3322, 2950, 2932, 2864, 1733, 1447, 1374, 1043, 957, 802; HRMS (EI): m/z calcd for $C_{16}H_{24}O^+$: 232.1825, found: 232.1827.

2-(4-(2-Methylprop-1-enyl)-5-(propan-2-ylidene)cyclopent-1-enyl)ethanol (18g)



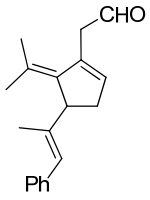
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.73 (s, 1H), 5.00 (ddt, *J* = 9.6, 2.8, 1.4 Hz, 1H), 3.73 (m, 2H), 3.59 (t, *J* = 8.7 Hz, 1H), 2.72-2.59 (m, 3H), 1.93-1.90 (m, 1H), 1.86 (s, 3H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.66-1.65 (m, 6H), 1.44 (s, 1H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 142.4, 141.2, 134.1, 130.1, 128.9, 123.3, 62.1, 42.8, 38.5, 35.4, 25.8, 23.7, 21.3, 18.2 ppm; IR (neat, ν/cm^{-1}): 3307, 2968, 2912, 2854, 1444, 1374, 1038, 795; HRMS (EI): m/z calcd for $C_{14}H_{22}O^+$: 206.1671, found: 206.1671.

2-(4-(2-Methylprop-1-enyl)-5-(prop-1-en-2-yl)cyclopent-1-enyl)ethanol (18g')



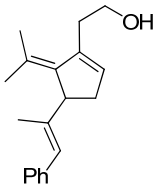
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.59 (s, 1H), 5.47 (s, 1H), 4.76-4.74 (m, 2H), 3.70-3.59 (m, 2H), 2.99-2.97 (m, 1H), 2.66-2.60 (m, 1H), 2.17-2.03 (m, 2H), 1.79 (s, 3H), 1.77 (s, 3H), 1.75-1.62 (m, 2H), 1.59 (m, 3H), 1.27 (s, 1H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 148.1, 141.8, 136.2, 127.9, 120.9, 111.9, 63.9, 61.9, 39.8, 39.7, 39.2, 27.2, 20.3, 19.2 ppm; IR (neat, ν/cm^{-1}): 3364, 2963, 2923, 2858, 2360, 1644, 1448, 1379, 1260, 1055, 884, 799; HRMS (EI): m/z calcd for $C_{14}H_{22}O^+$: 206.1670, found: 206.1671.

(*E*)-2-(4-(1-Phenylprop-1-en-2-yl)-5-(propan-2-ylidene)cyclopent-1-enyl)acetaldehyde (17h)



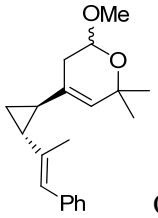
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (t, *J* = 2.2 Hz, 1H), 7.33-7.29 (m, 2H), 7.23-7.16 (m, 3H), 6.29 (s, 1H), 5.83 (s, 1H), 3.65 (d, *J* = 8.6 Hz, 1H), 3.52 (m, 2H), 2.83 (dd, *J* = 18.0, 8.8 Hz, 1H), 2.21 (d, *J* = 17.4 Hz, 1H), 1.85 (s, 3H), 1.78 (d, *J* = 1.1 Hz, 3H), 1.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6, 144.2, 139.5, 138.6, 136.9, 136.5, 128.8, 128.0, 125.8, 125.3, 124.2, 52.5, 46.4, 37.2, 23.7, 21.0, 14.8 ppm; IR (neat, ν/cm^{-1}): 3021, 2976, 2910, 2850, 2717, 2366, 2340, 1724, 1598, 1491, 1444, 1260, 1025, 911, 796, 731, 699; HRMS (EI): m/z calcd for $C_{19}H_{22}O^+$: 266.1667, found: 266.1671.

(*E*)-2-(4-(1-Phenylprop-1-en-2-yl)-5-(propan-2-ylidene)cyclopent-1-enyl)ethanol (18h)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-7.28 (m, 2H), 7.22-7.15 (m, 3H), 6.24 (s, 1H), 7.76 (s, 1H), 3.85-3.78 (m, 2H), 3.60 (d, *J* = 8.3 Hz, 1H), 2.83-2.67 (m, 3H), 2.17-2.13 (m, 1H), 1.93 (s, 3H), 1.76 (d, *J* = 1.5 Hz, 3H), 1.74 (s, 3H), 1.50 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 141.5, 139.5, 138.7, 133.8, 128.8, 127.9, 125.8, 124.8, 123.7, 61.5, 52.5, 36.8, 34.8, 23.8, 21.1, 15.0 ppm; IR (neat, ν/cm^{-1}): 3386, 2973, 2927, 2356, 2332, 1702, 1445, 1359, 1156, 1047, 746, 700; HRMS (ESI): m/z calcd for $C_{19}H_{24}NaO^+$: 291.1725, found: 291.1725.

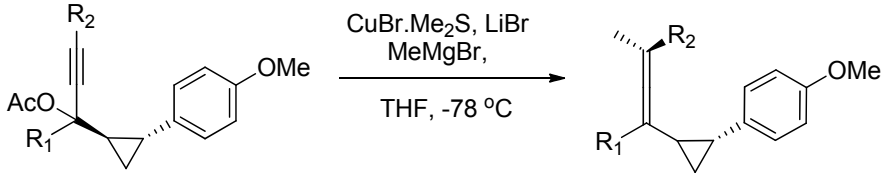
(*E*)-6-Methoxy-2,2-dimethyl-4-(2-(1-phenylprop-1-en-2-yl)cyclopropyl)-5,6-dihydro-2*H*-pyran (19) (carbon signals are missing due to overlapping)



Obtained as a 1:1 mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-7.28 (m, 4H), 7.23-7.15 (m, 6H), 6.31 (s, 2H), 5.40-5.37 (m, 2H), 4.77 (t, *J* = 5.8 Hz, 1H), 4.76 (t, *J* = 5.8 Hz, 1H), 3.47 (s, 6H), 2.16-1.98 (m, 4H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.77 (d, *J* = 1.5 Hz, 3H), 1.63-1.50 (m, 4H), 1.32 (d, *J* = 3.5 Hz, 6H), 1.27 (d, *J* = 4.7 Hz, 6H), 1.00-0.95 (m, 2H), 0.94-0.89 (m,2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 138.2, 138.2, 131.4, 131.3, 128.8, 128.0, 126.8, 126.6, 125.9, 124.0, 123.9, 93.4 (2xC), 73.4, 55.6, 55.5, 32.2, 31.9, 29.7 (2xC), 27.8, 27.7, 27.5, 24.7, 24.6, 16.0, 15.9, 10.8, 10.6 ppm.

5 Preparation and characterization of cyclopropyl allenes and cyclization products

5.1 General procedure for the preparation of cyclopropyl allenes

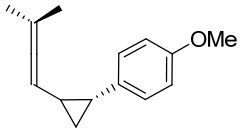


To a solution of $CuBr.Me_2S$ (3.0 equiv.) and LiBr (3.0 equiv.) in THF (0.6 M) at -78 °C, MeMgBr (1.0 M in butylether, 2.0 equiv.) was added dropwise. The mixture was stirred at -78 °C for 20 minutes. A solution of the corresponding acetate (1.0 equiv.) in THF (0.6 M) was added dropwise. The mixture was stirred at -78 °C for 15 minutes and then warmed up to room temperature and stirred for 2 hours. The reaction was quenched with an aqueous NH_4Cl/NH_4OH (1/1) solution.

The resulting mixture was extracted with diethyl ether and the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (Hexane) to give the corresponding allenes.

5.2 Characterization of the cyclopropyl allenes

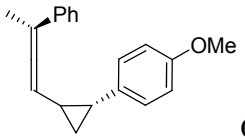
1-Methoxy-4-(2-(3-methylbuta-1,2-dienyl)cyclopropyl)benzene (20a)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.98 (m, 1H), 3.78 (s, 3H), 1.82-1.76 (m, 1H), 1.71 (d, *J* = 3.3 Hz, 3H), 1. 70 (d, *J* = 3.3 Hz, 3H) 1.45-1.38 (m, 1H), 1.08-1.03 (m, 1H), 1.00-0.92 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.0, 157.6, 134.8, 126.7, 113.8, 97.2, 92.2, 55.3, 24.9, 21.9, 20.9, 20.8, 16.5 ppm; IR (neat, ν/cm^{-1}): 2994, 2978, 2933, 2907, 2833, 1612, 1512, 1442, 1244, 1178, 1035, 821, 543; HRMS (EI): m/z calcd for $C_{15}H_{18}O^+$: 214.1357, found: 214.1358.

1-Methoxy-4-2-(3-phenylbuta-1,2-dienyl)cyclopropyl)benzene (20b)

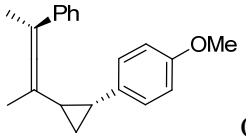
(carbon signals are missing due to overlapping)



Obtained as a 1:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43-7.41 (m, 4H), 7.35-7.30 (m, 4H), 7.22-7.18 (m, 2H), 7.04-7.01 (m, 4H), 6.84-6.81 (m, 4H), 5.54-5.47 (m, 2H), 3.78 (s, 6H), 2.12 (d, *J* = 2.9 Hz, 3H), 2.11 (d, *J* = 2.9 Hz, 3H), 1.95-1.89 (m, 2H), 1.58-1.52 (m, 2H), 1.16-1.05 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.8, 203.7, 157.8, 137.4, 137.3, 134.5, 134.4, 128.3, 128.2, 126.8, 126.7, 126.6, 125.7, 125.6, 113.8, 102.6, 102.5, 96.4, 96.3, 55.3, 25.2, 24.9, 21.5, 21.2, 17.3, 16.7, 16.5 ppm; IR (neat, ν/cm^{-1}): 3056, 2999, 2935, 2246, 1612, 1514, 1492, 1442, 1247, 1178, 1035, 907, 730; HRMS (EI): m/z calcd for $C_{20}H_{20}O^+$: 276.1516, found: 276.1514.

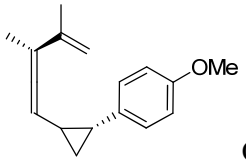
1-Methoxy-4-(2-(4-phenylpenta-2,3-dien-2-yl)cyclopropyl)benzene (20c)

(carbon signals are missing due to overlapping)



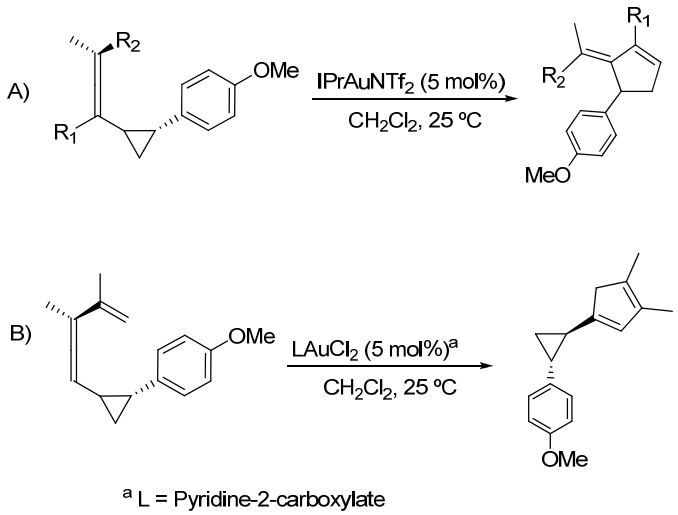
Obtained as a 1:1 mixture of isomers. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.39-7.36 (m, 4H), 7.32-7.28 (m, 4H), 7.20-7.16 (m, 2H), 7.03-7.01 (m, 4H), 6.81-6.79 (m, 4H), 3.76 (s, 6H), 2.08 (s, 6H), 1.96-1.91 (m, 2H), 1.89 (s, 3H), 1.88 (s, 3H), 1.49-1.45 (m, 2H), 1.11-1.02 (m, 4H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 201.5, 201.4, 158.4, 138.9, 138.8, 135.4, 135.3, 128.8, 128.7, 127.4, 126.9, 126.2, 126.1, 114.3, 104.4, 104.3, 102.1, 102.0, 55.8, 26.3, 26.1, 25.2, 25.0, 18.7, 18.6, 17.8, 17.7, 16.2, 16.1 ppm; IR (neat, ν/cm^{-1}): 2994, 2924, 2854, 1610, 1513, 1491, 1442, 1245, 1177, 1037, 952, 824, 759, 694; HRMS (EI): m/z calcd for $C_{21}H_{22}O^{+}$: 290.1672, found: 290.1671.

1-(2-(3,4-Dimethylpenta-1,2,4-trienyl)cyclopropyl)-4-methoxybenzene (20d)



Obtained as a mixture 1:1 of isomers. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.02-7.00 (m, 4H), 6.83-6.80 (m, 4H), 5.38-5.37 (m, 2H), 4.94-4.92 (m, 4H), 3.77 (s, 6H), 1.92-1.90 (m, 2H), 1.90 (d, *J* = 2.7, Hz, 3H), 1.89 (d, *J* = 2.7 Hz, 3H), 1.86 (d, *J* = 7.5 Hz, 6H), 1.50-1.45 (m, 2H), 1.14-1.07 (m, 2H), 1.04-1.00 (m, 2H) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 205.5, 205.4, 158.4, 141.8, 141.7, 135.1, 127.4, 127.3, 114.3, 114.3, 111.2, 111.1, 105.3, 95.6, 95.5, 55.8, 25.3, 25.1, 22.0, 22.0, 21.9, 21.8, 17.3, 17.2, 16.8, 16.7 ppm; IR (neat, ν/cm^{-1}): 3010, 2949, 2834, 1615, 1513, 1441, 1299, 1245, 1177, 1036, 907, 882, 823; HRMS (EI): m/z calcd for $C_{17}H_{20}O^{+}$: 240.1517, found: 240.1517.

5.3 General procedure for the cyclization of 3-cyclopropyl allenes

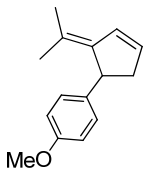


A) To a solution of the corresponding 3-cyclopropyl allene (1.0 equiv.) in CH_2Cl_2 (0.05 M), $IPrAuNTf_2$ (0.05 equiv.) was added in one portion. The mixture was stirred at room temperature for 30 minutes. The reaction was quenched with triethylamine (0.05 equiv.). The solution was dried under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 25:1) to give the corresponding cyclopentenes in 67-92% yield.

B) To a solution of 1-(2-(3,4-dimethylpenta-1,2,4-trienyl)cyclopropyl)-4-methoxybenzene (**20d**) (1.0 equiv.) in CH_2Cl_2 (0.05 M), dichloro(pyridine-2-carboxylato)gold (III) (0.05 equiv.) was added in one portion. The mixture was stirred at room temperature for 5 minutes. The reaction was quenched with triethylamine (0.05 equiv.). The solution was dried under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 25:1) to give the **22** in 96% yield.

5.4 Characterization of cyclization products

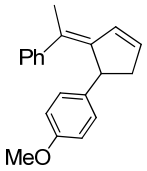
1-Methoxy-4-(2-(propan-2-ylidene)cyclopent-3-enyl)benzene (21a)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09-7.05 (m, 2H), 6.81-6.78 (m, 2H), 6.51 (dt, *J* = 5.5, 2.1 Hz, 1H), 5.91-5.89 (m, 1H), 3.92-3.90 (d, *J* = 8.6 Hz, 1H), 3.78 (s, 3H), 3.08 (dd, *J* = 17.8, 8.6 Hz, 1H), 2.32 (dd, *J* = 17.8, 1.0 Hz, 1H), 1.81 (s, 3H), 1.48 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 143.3, 139.9, 132.5, 131.5, 127.8, 123.3, 113.7, 55.2, 44.8, 43.8, 21.3,

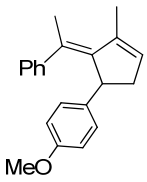
21.2 ppm; IR (neat, ν/cm^{-1}): 3062, 2984, 2953, 2908, 2840, 1609, 1509, 1441, 1176, 1037, 907, 730; HRMS (EI): m/z calcd for $C_{15}H_{18}O^+$: 214.1359, found: 214.1358.

(*Z*)-1-Methoxy-4-(2-(1-phenylethylidene)cyclopent-3-enyl)benzene (21b)



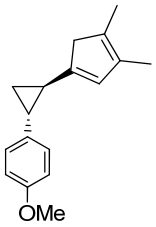
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13-7.07 (m, 3H), 6.88-6.86 (m, 2H), 6.65-6.63 (m, 3H), 6.59-6.56 (m, 2H), 6.13 (dt, *J* = 5.5, 2.6 Hz, 1H), 3.84 (d, *J* = 8.1 Hz, 1H), 3.72 (s, 3H), 3.07-3.00 (m, 1H), 2.39-2.34 (m, 1H), 2.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 146.2, 144.1, 140.0, 135.3, 131.8, 127.8, 127.7, 127.6, 125.8, 113.2, 55.2, 44.7, 43.4, 21.9 ppm; IR (neat, ν/cm^{-1}): 3056, 2921, 2832, 2366, 1509, 1301, 1243, 1176, 1037, 916, 827, 745, 700; HRMS (EI): m/z calcd for $C_{20}H_{20}O^+$: 276.1508, found: 276.1514.

(*E*)-1-Methoxy-4-(3-methyl-2-(1-phenylethylidene)cyclopent-3-enyl)benzene (21c)



^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.14-7.06 (m, 3H), 6.83-6.81 (m, 2H), 6.61-6.55 (m, 4H), 5.82 (s, 1H), 3.82-3.76 (m, 1H), 3.71 (s, 3H), 2.83-2.76 (m, 1H), 2.23 (d, *J* = 1.6 Hz, 3H), 2.18 (s, 3H), 2.08-2.03 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 157.9, 147.0, 145.9, 141.9, 141.3, 135.4, 129.8, 128.4, 128.3, 128.2, 126.1, 113.6, 55.6, 48.4, 41.0, 21.9, 18.8 ppm; IR (neat, ν/cm^{-1}): 3025, 2926, 2834, 1609, 1509, 1440, 1242, 1175, 1036, 828, 762, 700; HRMS (EI): m/z calcd for $C_{21}H_{22}O^+$: 290.1670, found: 290.1671.

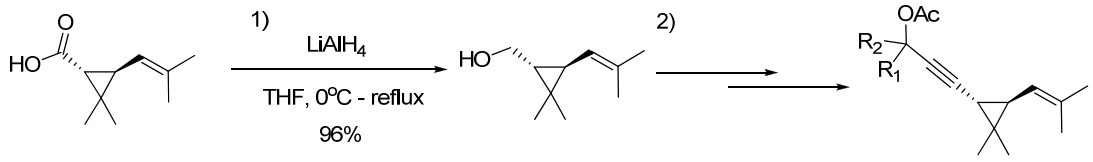
1-(2-(3,4-Dimethylcyclopenta-1,3-dienyl)cyclopropyl)-4-methoxybenzene (22)



^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.02-7.00 (m, 2H), 6.82-6.80 (m, 2H), 5.96 (s, 1H), 3.77 (s, 3H), 2.76 (s, 2H), 1.94-1.90 (m, 1H), 1.89 (s, 3H), 1.86-1.82 (m, 1H), 1.81 (d, *J* = 0.8 Hz, 3H), 1.22-1.18 (m, 1H), 1.17-1.13 (m, 1H) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 158.4, 146.7, 135.4, 134.9, 132.8, 129.7, 127.1, 114.3, 55.8, 45.9, 26.9, 25.1, 17.9, 13.4, 12.8 ppm; IR (neat, ν/cm^{-1}): 3041, 2998, 2955, 2910, 2855, 2833, 1612, 1512, 1440, 1376, 1243, 1177, 1035, 872, 824, 526; HRMS (EI): m/z calcd for $C_{17}H_{20}O^+$: 240.1517, found: 240.1514.

6 Preparation and characterization of chiral probes including HPLC chromatograms

6.1 Preparation of chiral propargyl acetates



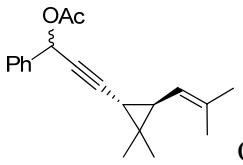
[trans-(+)-Chrysanthemic acid]

(1R,3R)-trans-2,2-Dimethyl-3-(2-methyl-1-propenyl) cyclopropane-1-carboxylic acid (> 99% ee)

1) To a solution of $LiAlH_4$ (1.0 equiv) in THF (0.3 M) at 0 °C, a solution of trans-Chrysanthemic acid (1.0 equiv) in THF (0.6 M) was added dropwise. The mixture was stirred at 0 °C for 10 minutes. Then the reaction was heating to reflux and stirred for 12 hours. The reaction was quenched with water, a solution of NaOH (15% v/v) and water again. The mixture was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (Hex:AcOEt 3:1) to give the corresponding alcohol in 96% yield.
2) The remaining steps for the formation of the corresponding secondary and tertiary propargyl acetates were performed according to previously described general procedures.

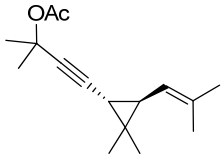
6.2 Characterization of propargyl acetates

(1*R*,3*R*)-3-(2,2,-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)-1-phenylprop-2-ynyl acetate (23)



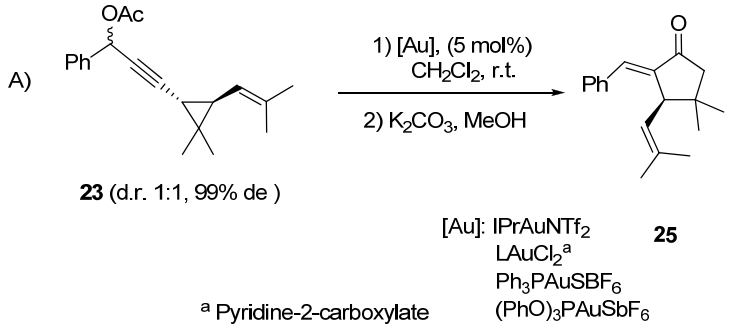
Obtained as a 1:1 diastereomeric mixture in the propargyl position. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.53-7.51 (m, 4H), 7.39-7.31 (m, 6H), 6.48 (m, 2H), 4.84-4.82 (m, 2H), 2.09 (s, 3H), 2.08 (s, 3H), 1.71 (s, 12H), 1.55-1.50 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.09-1.07 (m, 2H), 1.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ =169.9, 137.8 (2xC), 135.1 (2xC), 128.7 (2xC), 128.5, 127.7 (2xC), 121.7 (2xC), 88.9 (2xC), 75.3 (2xC), 66.3, 33.8 (2xC), 25.6, 25.3 (2xC), 23.2 (2xC), 22.2 (2xC), 21.2, 21.0, 18.5 ppm; IR (neat, ν/cm^{-1}): 2923, 2362, 2323, 2235, 1740, 1455, 1369, 1014, 955, 754, 697; HRMS (ESI): m/z calcd for $C_{20}H_{24}NaO_2^+$: 319.1674, found: 319.1674.

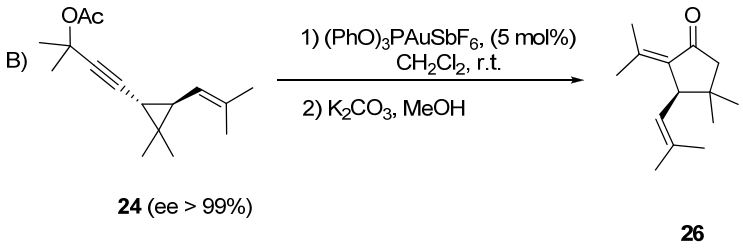
(1*R*,3*R*)-4-(2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)-2-methylbut-3-yn-2-yl acetate (24)



^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.82-4.80 (m, 1H), 1.99 (s, 3H), 1.70 (s, 6H), 1.64-1.63 (m, 1H), 1.63 (s, 6H), 1.45 (dd, *J* = 7.9, 5.1 Hz, 1H), 1.21 (s, 3H), 1.03 (s, 3H), 1.00 (d, *J* = 5.1 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 135.4, 122.6, 85.7, 80.5, 73.4, 34.3, 30.0, 29.9, 26.2, 25.6, 23.6, 22.8, 22.7, 21.6, 19.1 ppm; IR (neat, ν/cm^{-1}): 2973, 2927, 2858, 2249, 1735, 1369, 1251, 1136, 1017, 907, 731, 648; $[\alpha]_D^{24}$ = 67.5^o (c = 0.81, $CHCl_3$); HRMS (ESI): m/z calcd for $C_{16}H_{24}NaO_2^+$: 271.1667, found: 271.1668.

6.3 General procedure for the preparation of ketones 25 and 26





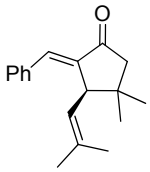
A) To a solution of **23** (1.0 equiv.) in CH_2Cl_2 (0.05 M) at room temperature, gold catalyst (0.05 equiv.) was added. The solution was stirred at room temperature for 30 minutes. The reaction was diluted with methanol. Then, potassium carbonate (2.0 equiv.) was added. The mixture was stirred at room temperature for 15 minutes. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 50:1) to give **25**.

B) To a solution of **24** (1.0 equiv.) in CH_2Cl_2 (0.05 M) at room temperature, $(PhO)_3PAuSbF_6$ (0.05 equiv.) was added. The solution was stirred at room temperature for 30 minutes.

The reaction was diluted with methanol. Then, potassium carbonate (2.0 equiv.) was added. The mixture was stirred at room temperature for 15 minutes. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hex:AcOEt 50:1) to give **26**.

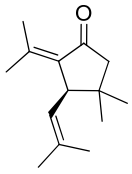
6.4 Characterization of ketones 25 and 26

(2*R*)-(*E*)-2-Benzylidene-4,4-dimethyl-3-(2-methylprop-1-enyl)cyclopentanone (25)



^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46-7.43 (m, 3H), 7.36-7.32 (m, 2H), 4.93 (dq, *J* = 10.4, 1.4 Hz, 1H), 3.58 (d, *J* = 10.7 Hz, 1H), 2.34 (d, *J* = 17.3 Hz, 1H), 2.16 (dd, *J* = 17.4, 1.1 Hz, 1H), 1.84 (d, *J* = 1.3 Hz, 3H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.2, 141.0, 134.9, 133.9, 133.7, 130.7, 129.0, 128.2, 123.0, 51.0, 50.8, 38.7, 29.4, 25.7, 24.4, 18.5 ppm; IR (neat, ν/cm^{-1}): 2954, 2921, 2869, 2249, 1715, 1621, 1448, 1188, 909, 731, 694; $[\alpha]_D^{25}$ = 59.9^o (c = 0.53, $CHCl_3$); HRMS (ESI): m/z calcd for $C_{18}H_{22}NaO^+$: 277.1564, found: 277.1563.

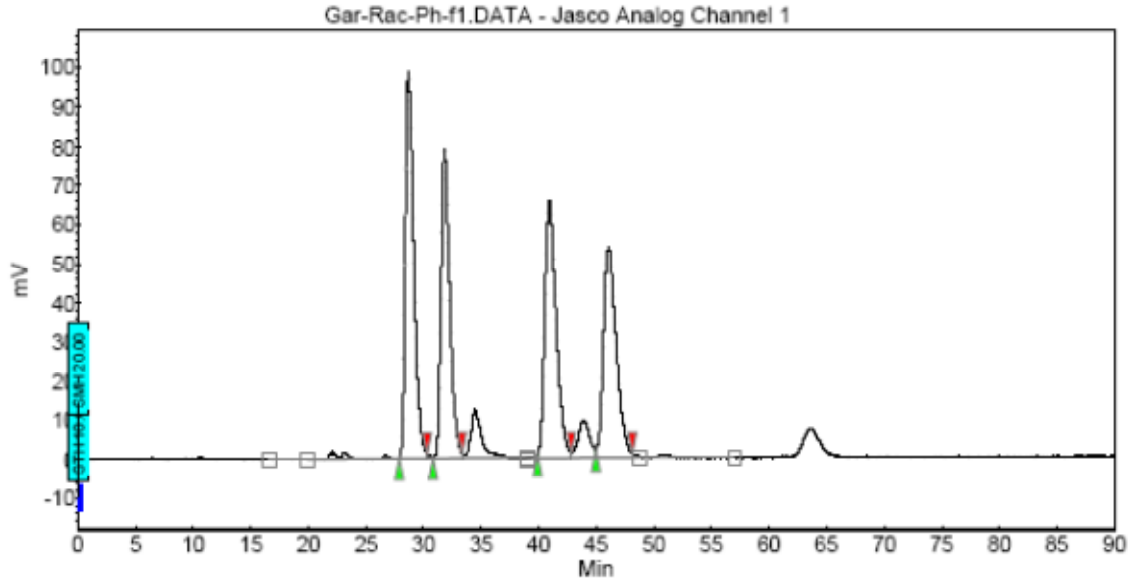
(2*R*)-4,4-Dimethyl-3-(2-methylprop-1-enyl)-2-(propan-2-ylidene)cyclopentanone (26)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.93-4.90 (m, 1H), 3.23 (d, *J* = 10.8 Hz, 1H), 2.27 (d, *J* = 17.2 Hz, 1H), 2.21 (s, 3H), 2.04 (dd, *J* = 17.2, 0.7 Hz, 1H), 1.73 (s, 6H), 1.71 (d, *J* = 1.1 Hz, 3H), 1.01 (s, 3H), 0.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.0, 149.3, 135.9, 131.4, 124.2, 53.2, 51.5, 36.7, 29.7, 25.8, 24.6, 23.7, 21.1, 18.0 ppm; IR (neat, ν/cm^{-1}): 2954, 2926, 2874, 1702, 1626, 1445, 1367, 1266, 1188, 908, 731, 648; $[\alpha]_D^{23}$ = - 20.5^o (c = 0.30, $CHCl_3$); HRMS (EI): m/z calcd for $C_{14}H_{22}O^+$: 206.1673, found: 206.1671.

6.5 HPLC chromatograms

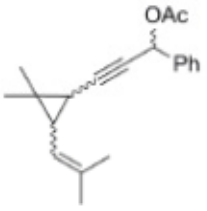
rac-3-(2,2,-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)-1-phenylprop-2-ynyl acetate (23)



Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	28.683	28.39	98.6	85.1	28.393
2	UNKNOWN	31.830	23.24	79.3	69.7	23.245
3	UNKNOWN	40.897	25.05	65.8	75.1	25.053
4	UNKNOWN	46.043	23.31	54.0	69.9	23.309
Total			100.00	297.6	299.8	100.000

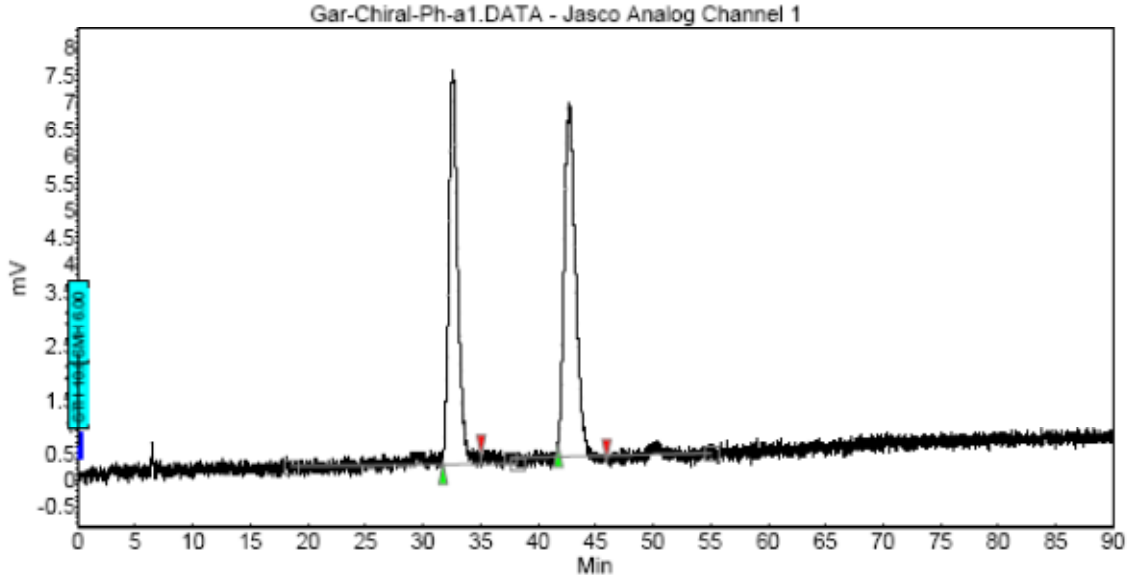
CHROMATOGRAM METHOD REPORT :

Acquisition :
Run Name : Gar-Rac-Ph-f1
Description :
Column: OD-H, iPrOH/n-Hexane=0.1:99.9, 0.5 ml/min
Run Time : 90.00
Vial : 4



rac-**23**

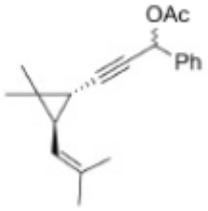
(1*R*,3*R*)-3-(2,2,-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)-1-phenylprop-2-ynyl acetate (23)



Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	32.570	47.23	7.3	6.6	47.227
2	UNKNOWN	42.677	52.77	6.6	7.4	52.773
Total			100.00	13.8	14.0	100.000

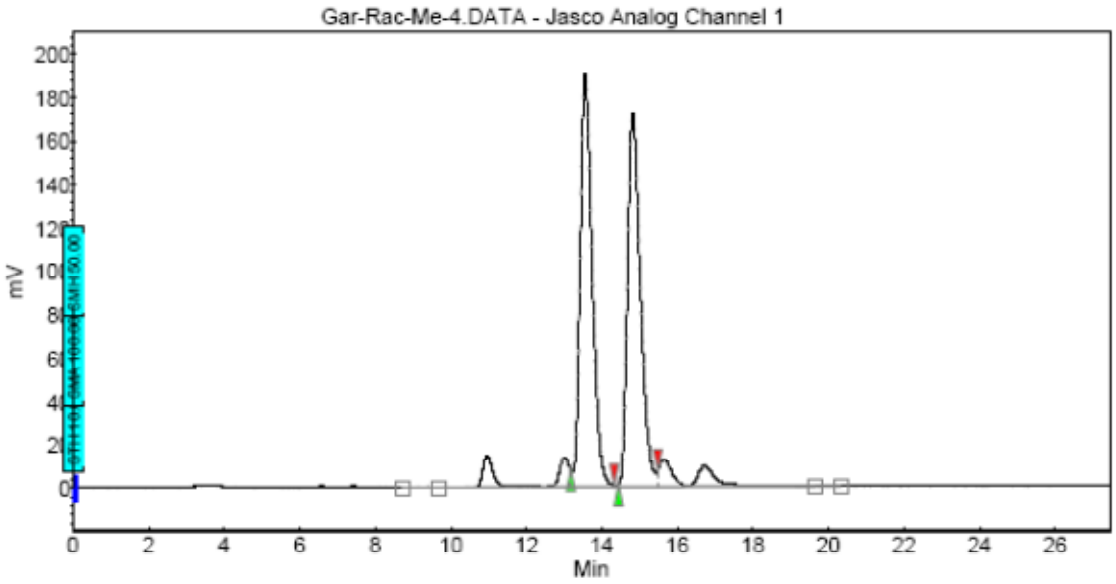
CHROMATOGRAM METHOD REPORT :

Acquisition :
Run Name : Gar-Chiral-Ph-a1
Description :
Column: OD-H, iPrOH/n-Hexane=0.1:99.9, 0.5 ml/min
Run Time : 90.00
Vial : 5



23

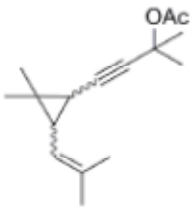
rac-4-(2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)-2-methylbut-3-yn-2-yl acetate (24)



Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	13.557	50.56	190.3	69.6	50.558
2	UNKNOWN	14.817	49.44	171.5	68.0	49.442
Total			100.00	361.9	137.6	100.000

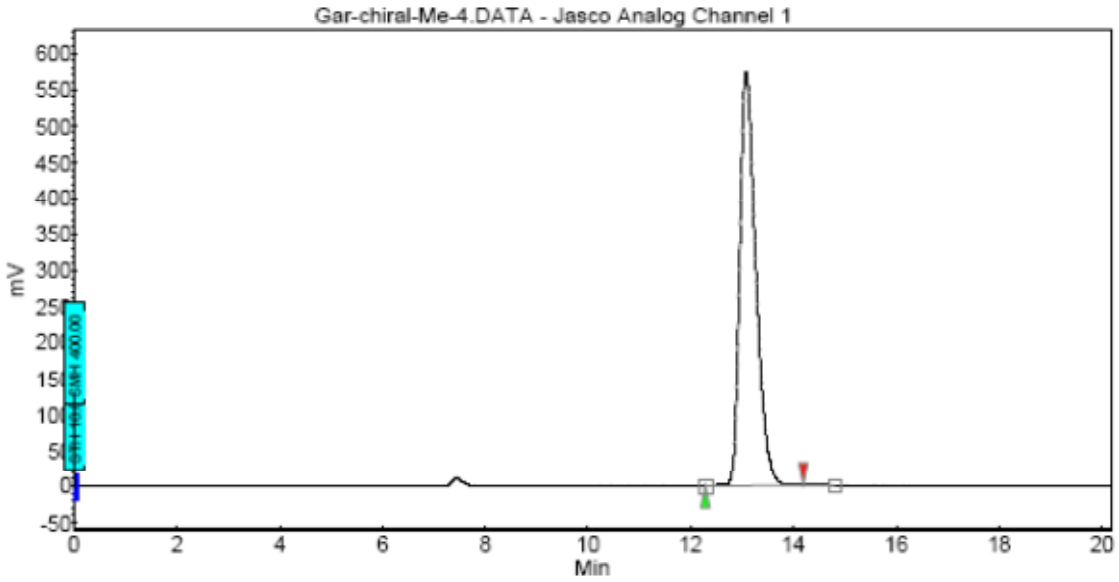
CHROMATOGRAM METHOD REPORT :

Acquisition :
Run Name : Gar-Rac-Me-4
Description :
Column: chiralcel OD-H, iPrOH/n-Hexane=0.1:99.9, 0.5 ml/min
Run Time : 75.00
Vial : 1



rac-**24**

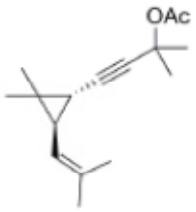
(1*R*,3*R*)-4-(2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)-2-methylbut-3-yn-2-yl acetate (24)



Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	13.073	100.00	573.7	209.7	100.000
Total			100.00	573.7	209.7	100.000

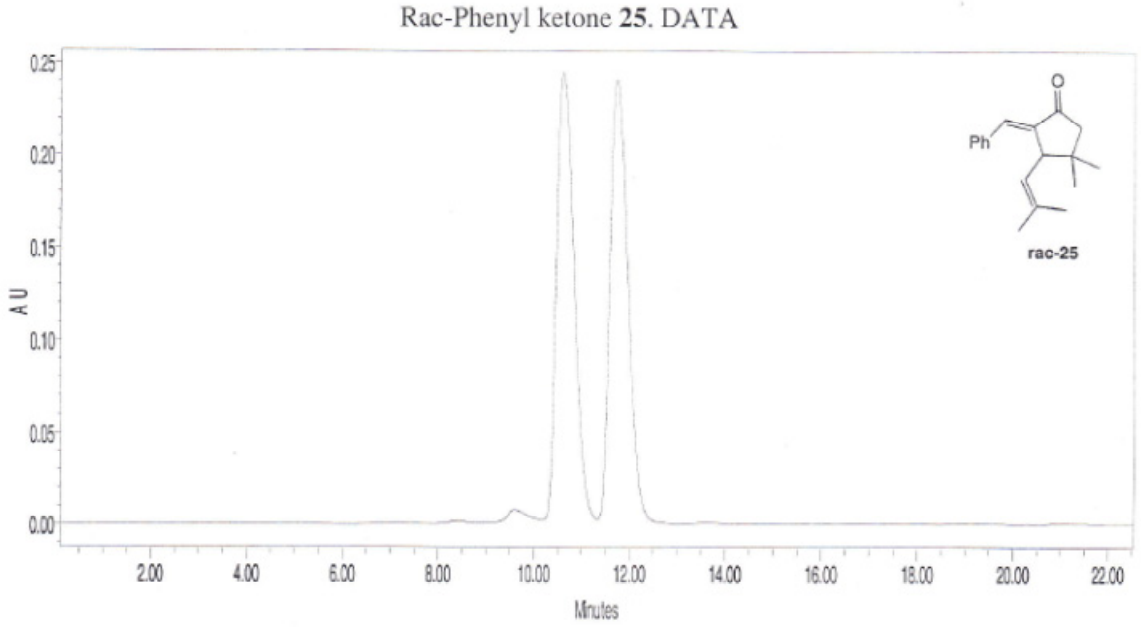
CHROMATOGRAM METHOD REPORT :

Acquisition :
Run Name : Gar-chiral-Me-4
Description :
Column: chiralcel OD-H, iPrOH/n-Hexane=0.1:99.9, 0.5 ml/min
Run Time : 75.00
Vial : 2



24

***rac*-2-Benzylidene-4,4-dimethyl-3-(2-methylprop-1-enyl)cyclopentanone (25)**

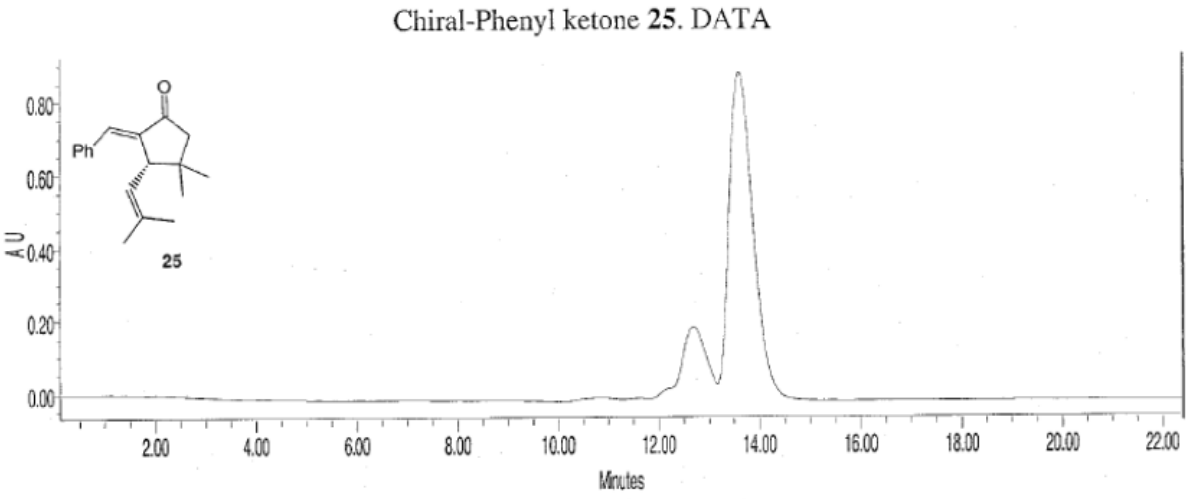


Index	Name	Retention Time	Area	% Area	Height	Int Type
1		8.360	31161	0.24	1193	BV
2		9.085	8396	0.07	680	VV
3		9.598	230979	1.80	7423	VV
4		10.614	6277269	49.03	244261	VV
5		11.738	6255330	48.86	240317	VB

CHROMATOGRAM METHOD REPORT:

Acquisition:
Run Name: GAR-GC-35-F20
Description:
Column: Chiralpak IB, iPrOH/n-Hexane = 2.0:98.0, 1.0 ml/min.
Run Time: 25.00
Vial : 1

(2*R*)-(*E*)-2-Benzylidene-4,4-dimethyl-3-(2-methylprop-1-enyl)cyclopentanone (25)



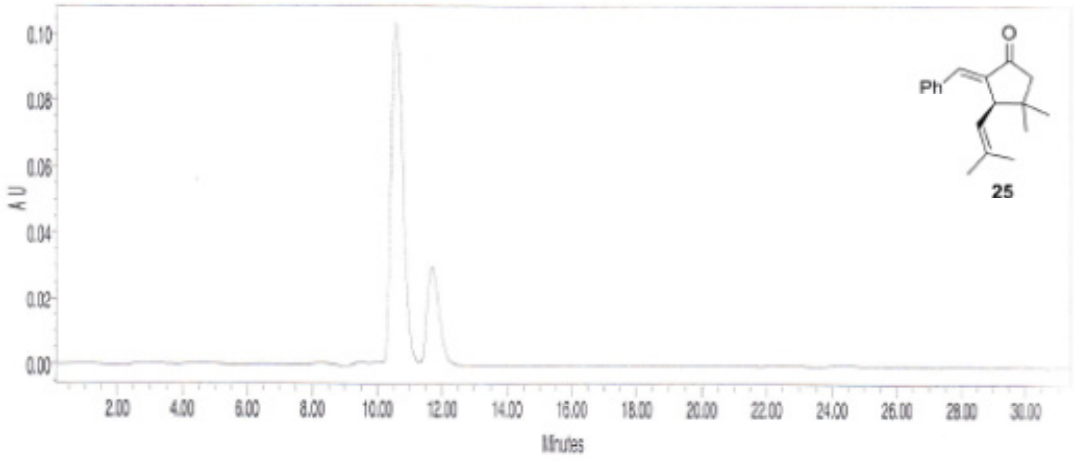
Index	Name	Retention Time	Area	% Area	Height	Int Type
1		12.688	7104014	19.28	201200	VV
2		13.614	29741454	80.72	900689	VB

CHROMATOGRAM METHOD REPORT:

Acquisition:
Run Name: GAR-GC-37-F34
Description:
Column: Chiralpak IB, iPrOH/n-Hexane = 2.0:98.0, 1.0 ml/min.
Run Time: 30.00
Vial : 1
Catalyst: $LAuCl_2$ [a]

[a] Pyridine-2-carboxylate

Chiral-Phenyl ketone **25**. DATA

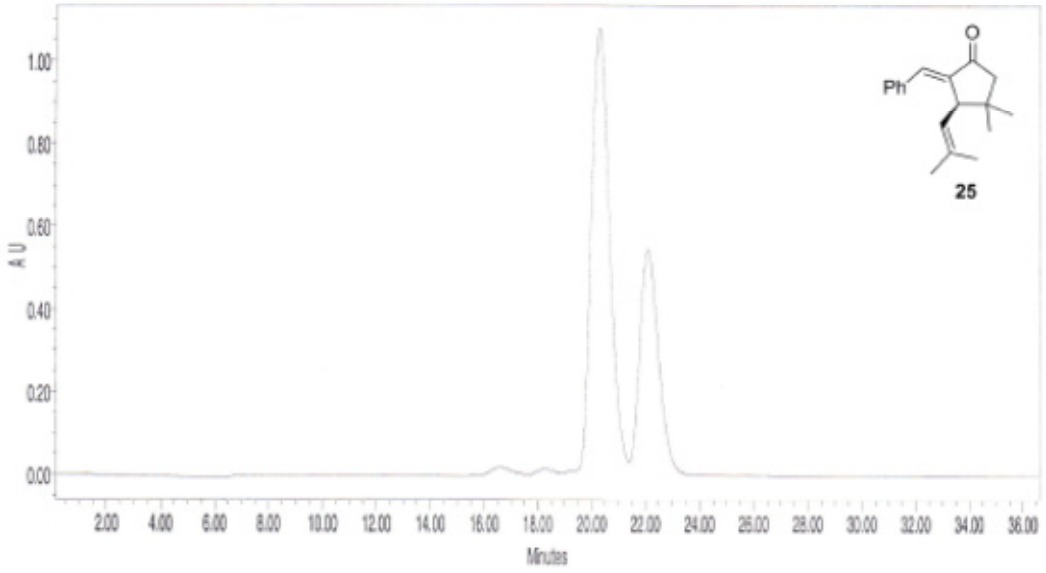


Index	Name	Retention Time	Area	% Area	Height	Int Type
1		9.485	19582	0.57	734	BV
2		10.563	2646372	77.16	103257	VV
3		11.683	763920	22.27	29584	VB

CHROMATOGRAM METHOD REPORT:

Acquisition:
Run Name: GAR-GC-36-F14
Description:
Column: Chiralpak IB, iPrOH/n-Hexane = 2.0:98.0, 1.0 ml/min.
Run Time: 30.00
Vial : 1
Catalyst: $IPrAuNTf_2$

Chiral-Phenyl ketone **25**. DATA

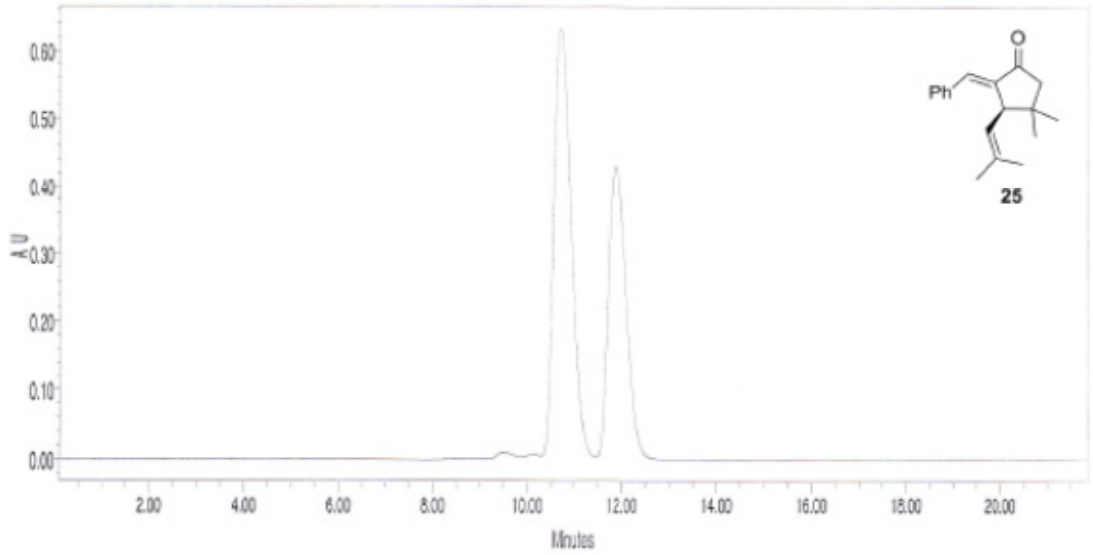


	Name	Retention Time	Area	% Area	Height	Int Type
1		8.539	1459270	1.78	3866	BV
2		16.605	1221716	1.49	20627	VV
3		18.269	785827	0.96	16576	VV
4		20.276	51917924	63.36	1080466	VV
5		22.094	26560357	32.41	544720	VB

CHROMATOGRAM METHOD REPORT:

Acquisition:
Run Name: GAR-GC-40-F15
Description:
Column: Chiralpak IB, iPrOH/n-Hexane = 2.0:98.0, 1.0 ml/min.
Run Time: 36.00
Vial : 1
Catalyst: $Ph_3PAuSbF_6$

Chiral-Phenyl ketone **25**. DATA

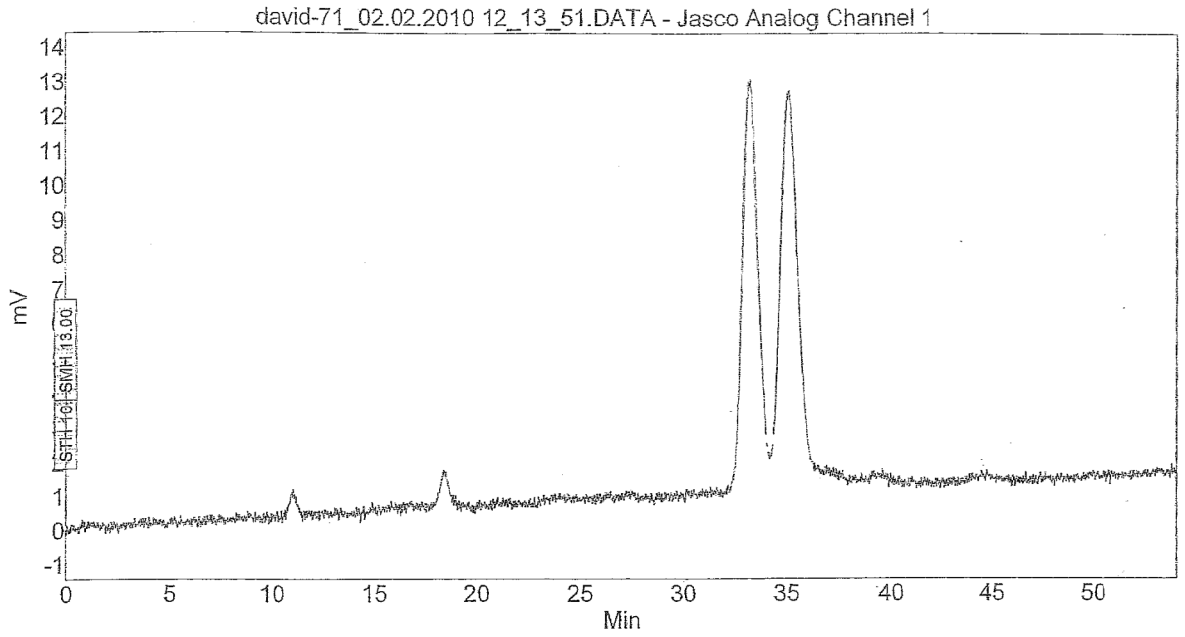


Index	Name	Retention Time	Area	% Area	Height	Int Type
1		8.502	37628	0.13	1185	BV
2		9.513	253509	0.91	10045	VV
3		10.125	139846	0.50	6853	VV
4		10.700	16290570	58.24	633084	VV
5		11.865	11250693	40.22	430450	VB

CHROMATOGRAM METHOD REPORT:

Acquisition:
Run Name: GAR-GC-39-F19
Description:
Column: Chiralpak IB, iPrOH/n-Hexane = 2.0:98.0, 1.0 ml/min.
Run Time: 25.00
Vial : 1
Catalyst: $(PhO)_3PAuSbF_6$

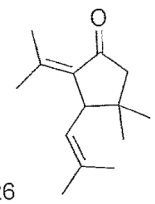
rac-4,4-Dimethyl-3-(2-methylprop-1-enyl)-2-(propan-2-ylidene)cyclopentanone (26)



Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	33.223	45.84	12.0	10.7	45.844
2	UNKNOWN	35.083	54.16	11.6	12.6	54.156
Total			100.00	23.6	23.3	100.000

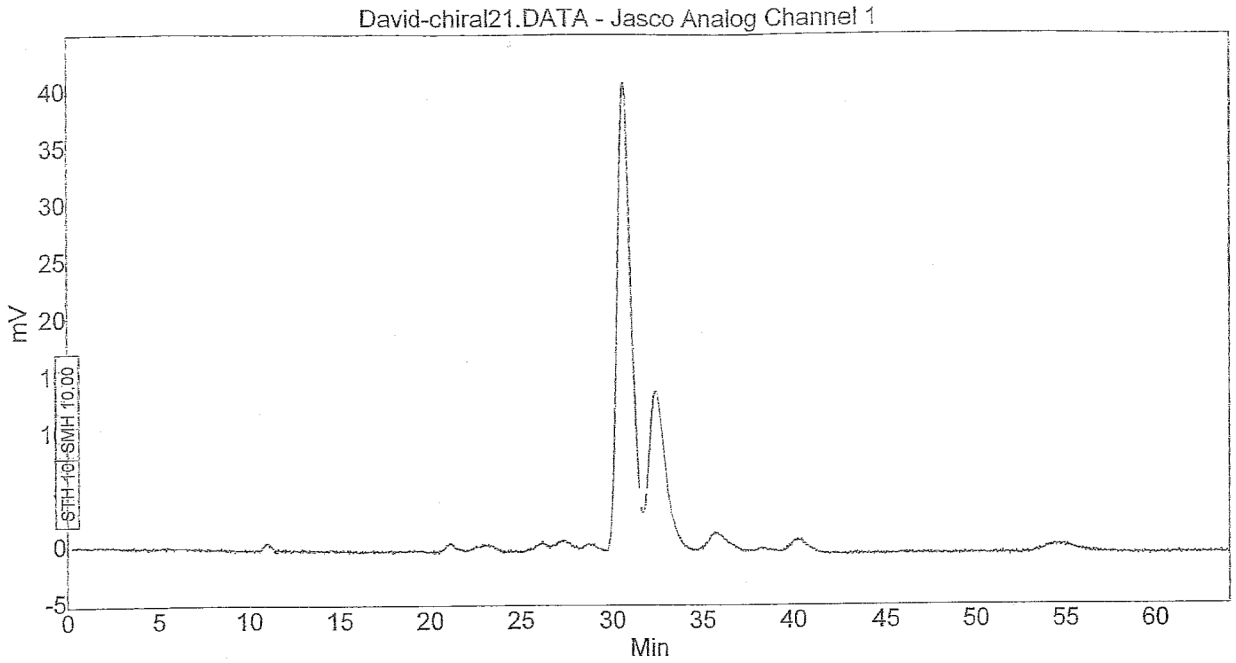
CHROMATOGRAM METHOD REPORT:

Acquisition:
Run Name: david-7
Description: Chiralcel OD-H, n-Hexane 0.3 ml/min.
Run time: 110.00
Vial: 7



rac-26

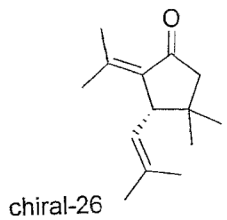
(2*R*)-4,4-Dimethyl-3-(2-methylprop-1-enyl)-2-(propan-2-ylidene)cyclopentanone (26)



Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	30.590	70.38	41.5	37.5	70.384
2	UNKNOWN	31.750	0.32	3.8	0.2	0.319
3	UNKNOWN	32.413	29.30	14.4	15.6	29.297
Total			100.00	59.6	53.2	100.000

CHROMATOGRAM METHOD REPORT:

Adquisition:
Run Name: David-chiral2
Description: Chiralcel OD-H, n-Hexane 0.3 ml/min.
Run Time: 110.00
Vial: 8



chiral-26

7. Computational Methods

Full Reference 20.

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M.A.; Cheeseman, J. R.; Montgomery, J. A. Jr.; Vreven, T.; Kudin, K. N.; Burant, J.C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision E.01, Gaussian, Inc., Wallingford CT, **2004**.

7.1 General Considerations

All reported structures were optimized at DFT level by using the B3LYP[6] hybrid functional as implemented in Gaussian 03.[7] Optimizations were carried out by using the standard 6-31G** basis set for C, H, O, N and P. The LANL2DZ basis set, which includes the relativistic effective core potential (ECP) of Hay and Wadt and employs a split-valence (double-ζ) basis set was used for Au.[8] All energy minima and transition structures were characterized by harmonic frequency analysis at the same level. The energies reported in this work include thermal and zero-point vibrational energy corrections (ZPVE). As corresponds to an intramolecular reaction, computed H and G values are within a narrow 0-2 kcal/mol energy difference for all stationary points, and point out the same reactivity trend. Therefore, only H values have been shown along the accompanying paper, and G values are listed in Table S1 and S2 of the present Supporting

[6] (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (b) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648–5652. (c) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem*. **1996**, *100*, 12974–12980.
[7] See Full Reference 20 in this page.
[8] (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys*. **1985**, *82*, 270-283. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284-298. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310.

Information. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies. The intrinsic reaction coordinates (IRC)[9] were followed to verify the energy profiles connecting each TS to the correct associated local minima. Solvent effects were included by single point energy calculations of the gas-phase structures with the self-consistent reaction field (SCRF) based on the IEF-PCM solvation model (CH_2Cl_2, as solvent, $\varepsilon = 8.93$, radii = UA0). In some cases, i.e. Scheme 12, the reoptimization of the structures was prohibitive due to the large number of atoms involved (Au = IPr), and single-point calculations were performed on the previously gas-phase optimized structures instead.[10]

7.2 Complementary Scheme 8

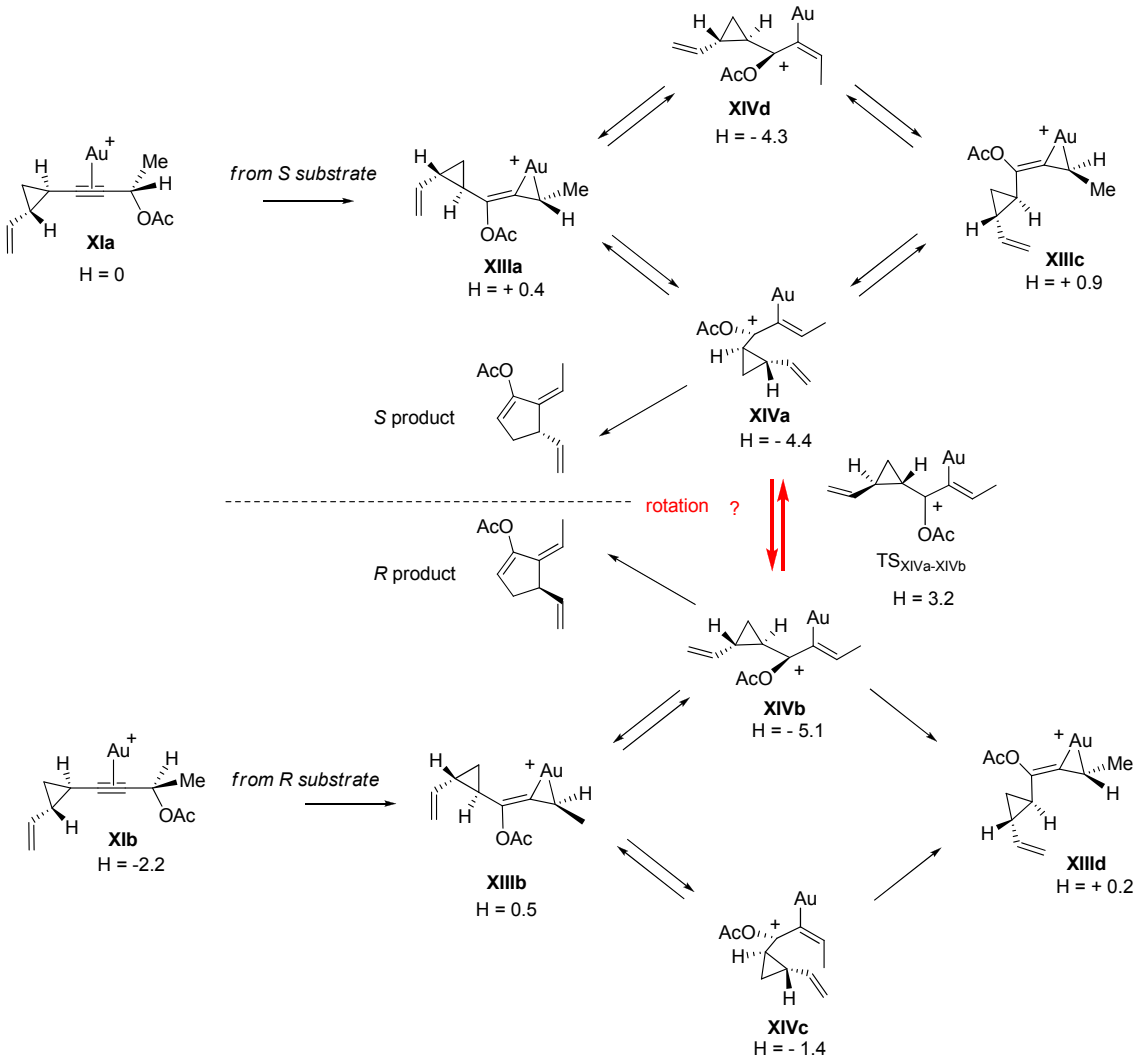
A more detailed version of Scheme 8 explaining the loss of chiral information at the propargylic position is presented here: Au(I)-complex of (*S*)-acetate **XIa** evolves to a gold coordinated allene **XIIIa** in an slightly endothermic process ($\Delta H = 0.4$ kcal/mol) (Scheme 1). **XIIIa** shows a clear "allene" character, with gold coordinated to the more external double bond and the four allenyl substituents disposed perpendicularly.

XIIIa is in equilibrium with two derivatives **XIVa** and **XIVd**, in which gold is coordinated to the internal double bond of the allene. These structures are more distorted and resemble an allylic carbocation although the substituents are located in perpendicular planes rather than in a common plane as one would expect from a normal cabocation. As summarized in the following scheme, **XIVa** and **XIVd** are thermodynamically more stable than **XIIIa** and **XIIIc**. Furthermore, only **XIVa** is reactive enough, since the rigidity of the double bond in **XIIIa-c** places the cyclopropyl unit and the cationic C atom in a non-reacting distance. From the (*R*) configured acetate in the starting material **XIb**, an analogous reaction pathway is observed. However, as indicated in Scheme 8 of the accompanying paper, the stereochemical information of the acetate at the propargylic position is lost by a low barrier transition state $\mathbf{TS_{XIVa\text{-}XIVb}}$ ($\Delta H^{\ddagger} = 3.2$ kcal/mol),

[9] Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem*. **1990**, *94*, 5523–5527.
[10] (a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys*. **1997**, *107*, 3032–3047. (b) Cossi, M.; Barone, V.; Mennuci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253–260. (c) Tomasi, J.; Mennucci, B.; Cancès, E. *J. Mol. Struct. (Theochem)*, **1999**, *464*, 211–226.

which converts **XVIa** into its enantiomer **XIVb** in a thermoneutral transformation (ΔH = -0.7 kcal/mol).

Complementary Scheme 8. Reaction coordinate diagram for the [3,3]-acetoxy migration of **XIa** to cationic intermediate **XIVa-d**. Calculations at the B3LYP/6-31G(d) (C, H, O, P), LANL2DZ (Au) level (+ ZPE corrected energies are given in kcal/mol). Au = (IPr)Au

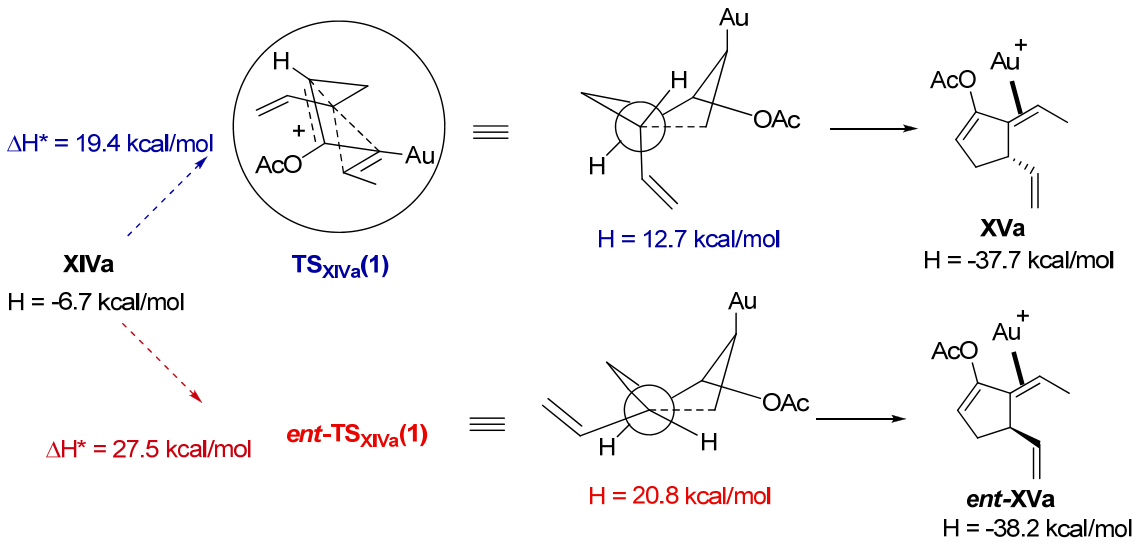


7.3 Further studies on the non-complete chirality transfer (Complementary to Schemes 9 and 12)

Transition states $\mathbf{TS_{XIVa\text{-}d}(1)}$ and $\mathbf{TS_{XVIa\text{-}d}(2)}$ shown in Scheme 9 retain the configuration at C6 bearing the vinyl stabilizing substituent. However, a potential mechanism where the cyclopropyl

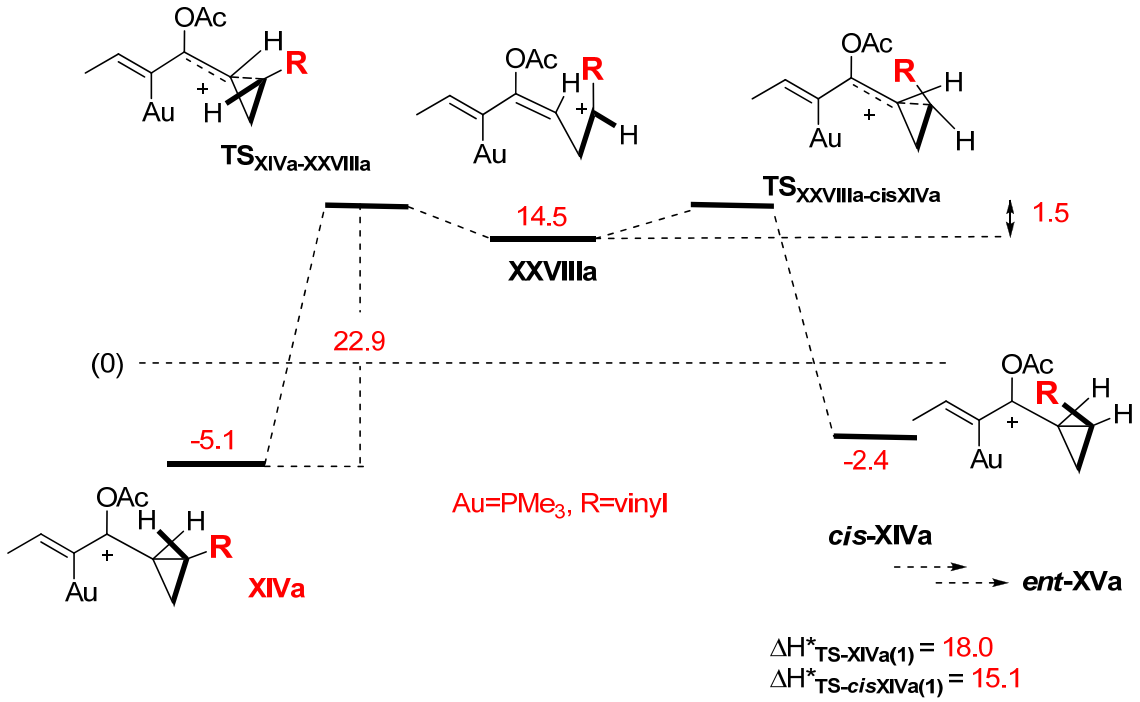
ring opening takes place inverting the configuration at C6, if comparable in energy to the one summarized in Scheme 9, could also explain the lack of complete chirality transfer observed experimentally in these transformations. Thus, a new transition state ***ent*-TS$_{XIVa}$(1)** was studied. ***ent*-TS$_{XIVa}$(1)** involves a slight rotation of the cyclopropyl compared to **TS$_{XIVa}$(1)**, which increases the strain (**H$_{ent\text{-}TS_{XIVa(1)}}$** = 20.8 kcal/mol vs. **HTS$_{XIVa(1)}$** = 12.7 kcal/mol; see Newman projections below). Thus, the activation energy for the cyclopropyl ring opening process raised to 27.5 kcal/mol (8 kcal/mol higher in energy than the ring opening with retention of configuration), which makes this mechanistic pathway unlikely, thus favoring the hypothesis of epimerization via cyclopropyl ring opening/ring closure summarized in Scheme 12 of the accompanying paper.

Complementary Scheme 9. Reaction coordinate diagram for the cyclopentannulation of **XIVa**. Calculations at the B3LYP/6-31G(d) (C, H, O, P), LANL2DZ (Au) level (+ ZPE corrected energies are given in kcal/mol. Au = $(Me_3P)Au$



Complementary calculations were performed using **XIVa** as a model to study the epimerization via ring-opening/ring closing reaction. The results, in agreement with those reported in Scheme 12 have been summarized below.

Complementary Scheme 12. Reaction coordinate diagrams for the cyclopropyl epimerization of **XIVa**. Calculations at the B3LYP/6-31G(d) (C, H, O, P), LANL2DZ (Au) level (+ ZPE corrected energies are given in kcal/mol; calculations considering solvent effects (CH_2Cl_2)). Au = (Me_3P)Au



7.4 Table S1. Absolute and relative enthalpies (H) and free Gibbs energies (G) of stationary points shown in the manuscript and in complementary scheme 8 of the supporting information

	Absolute enthalpy (H)[a]	Relative enthalpy (ΔH)[b]	Absolute Free energy (G)[c]	Relative Free energy (ΔG)[d]	Imaginary frequencies
XIa	-1872.546869	0	-1872.688997	0	
XIb	-1872.550349	-2.2	-1872.692087	-1.9	
$TS_{XIa-XIIa}$	-1872.536507	6.5	-1872.674659	9.0	-204.4
XIIa	-1872.547365	-0.3	-1872.685207	2.4	
$TS_{XIIa-XIIIa}$	-1872.542863	2.5	-1872.680716	5.2	-172.9
XIIIa	-1872.546170	0.4	-1872.685262	2.3	
XIIIb	-1872.546136	0.5	-1872.685453	2.2	
XIIIc	-1872.545405	0.9	-1872.680514	5.3	
XIIId	-1872.546587	0.2	-1872.685320	2.3	

$TS_{XIIIa-XIVa}$	-1872.540824	3.8	-1872.679951	5.7	-202.6
XIVa	-1872.553847	-4.4	-1872.690872	-1.2	
dcmXIVa	-1873.448375	-3.5			
XIVb	-1872.554962	-5.1	-1872.692305	-2.1	
dcmXIVb	-1873.451200	-5.3			
XIVc	-1872.551405	-2.9	-1872.690017	-0.6	
dcmXIVc	-1873.446855	-2.6			
XIVd	-1872.553681	-4.3	-1872.692743	-2.3	
dcmXIVd	-1873.449612	-4.3			
$TS_{XIVa-XIVb}$	-1872.548877	-1.3	-1872.684792	2.6	-32.2
TS_{XIVa}(1)	-1872.522096	15.5	-1872.658183	19.3	-125.9
dcmTS_{XIVa}(1)	-1873.420775	13.8			
TS_{XIVb}(1)	-1872.509989	23.1	-1872.644644	27.8	-128.9
dcmTS_{XIVb}(1)	-1873.412154	19.2			
TS_{XIVc}(1)	-1872.517992	18.1	-1872.655293	21.1	-167.0
dcmTS_{XIVc}(1)	-1873.415873	16.9			
TS_{XIVd}(1)	-1872.508512	24.1	-1872.643759	28.4	-51.5
dcmTS_{XIVd}(1)	-1873.410405	20.3			
TS_{XIVa}(2)	-1872.529568	10.9	-1872.663164	16.2	-291.0
dcmTS_{XIVa}(2)	-1872.531863	9.6			
TS_{XIVb}(2)	-1872.532733	8.9	-1872.666883	13.9	-130.8
dcmTS_{XIVb}(2)	-1873.432071	6.7			
TS_{XIVc}(2)	-1872.534129	8.0	-1872.667986	13.2	-222.9
dcmTS_{XIVc}(2)	-1873.429564	8.3			
TS_{XIVd}(2)	-1872.531919	9.4	-1872.668280	13.0	-148.0
dcmTS_{XIVd}(2)	-1873.429078	8.6			
XVa	-1872.605308	-36.7	-1872.738215	-36.7	
dcmXVa	-1873.501920	-37.1			
XVb	-1872.604841	-36.4	-1872.740542	-36.4	

dcmXVb	-1873.502515	-37.5			
XVc	-1872.601765	-34.4	-1872.740406	-32.3	
dcmXVc	-1873.499228	-35.4			
XVd	-1872.603278	-35.4	-1872.735110	-28.9	
dcmXVd	-1873.499843	-35.8			
XVIa	-1872.574145	-17.1	-1872.709645	-13.0	
dcmXVIa	-1873.473589	-19.3			
$TS_{XVIa-XVIIa}$	-1872.555709	-5.5	-1872.689324	-0.2	-684.3
dcm$TS_{XVIa-XVIIa}$	-1873.457296	-9.1			
XVIIa	-1872.603443	-35.5	-1872.739149	-31.5	
dcmXVIIa	-1873.501957	-37.2			
XVIII	-2140.645252	0	-2140.794002	0	
$TS_{XVIII-XIX}$	-2140.632990	7.7	-2140.783154	6.8	-189.7
XIX	-2140.641683	2.2	-2140.789399	2.9	
TS_{XIX-XX}	-2140.629876	9.6	-2140.776984	10.7	-390.2
XX	-2140.658710	-8.4	-2140.810151	-10.1	
TS_{XX-XXI}	-2140.634048	7.0	-2140.781677	7.7	-39.7
XXI	-2140.676398	-19.5	-2140.822623	-18.0	
$TS_{XXI-XXII}$	-2140.632552	8.0	-2140.780153	8.7	-304.0
XXII	-2140.695682	-31.6	-2140.838795	-28.1	
$TS_{XVIII-XXIII}$	-2140.633900	7.1	-2140.782831	7.1	-202.3
XXIII	-2140.644909	0.2	-2140.793916	0.0	
$TS_{XXIII-XXIV}$	-2140.639292	3.7	-2140.786892	4.5	-165.5
XXIV	-2140.649919	-2.9	-2140.799737	-3.6	
dcmXXIV	-2141.630771	-2.9			
$TS_{XXIV-XXV}$	-2140.633115	7.6	-2140.782270	7.4	-28.9
dcm$TS_{XXIV-XXV}$	-2141.617801	5.2			
XXV	-2140.701890	-35.5	-2140.849249	-34.7	
***ent*-XXV**	-2140.697645	-32.9	-2140.843326	-30.9	

XVIII'	-2179.935440	0	-2180.088307	0	
$TS_{(XVIII-XIX)'}$	-2179.922967	7.8	-2180.074334	8.8	-165.3
XIX'	-2179.933769	1.0	-2180.084402	2.4	
$TS_{(XIX-XX)'}$	-2179.922973	7.8	-2180.072245	10.1	-266.1
XX'	-2179.942990	-4.7	-2180.096279	-5.0	
$TS_{(XX-XXI)'}$	-2179.925194	6.4	-2180.075182	8.2	-37.7
XXI'	-2179.958868	-14.7	-2180.107158	-11.8	
$TS_{(XXI-XXII)'}$	-2179.916910	11.6	-2180.064924	14.7	-290.9
XXII'	-2179.976221	-25.6	-2180.124070	-22.4	
$TS_{(XVIII-XXIII)'}$	-2179.924876	6.6	-2180.075970	7.7	-207.2
XXIII'	-2179.936977	-1.0	-2180.088753	-0.3	
$TS_{(XXIII-XXIV)'}$	-2179.935071	0.2	-2180.086197	1.3	-121.9
XXIV'	-2179.938361	-1.8	-2180.090958	-1.7	
$TS_{(XXIV-XXV)'}$	-2179.918741	10.5	-2180.069464	11.8	-49.9
XXV'	-2179.984110	-30.5	-2180.134620	-29.1	
dcm$TS_{XXIV-XXVI}$	-2141.616203	6.2			
dcmXXVI	-2141.617609	5.3			
dcmTS_{XXVI-}*cis*XXIV	-2141.616857	5.8			
dcm*cis*-XXIV	-2141.625560	0.3			
dcm$TS_{}$*cis*XXIV-*ent*XXV	-2141.619656	4.0			
$TS_{XIVa-XXVIIa}$	-1872.511780	22.0	-1872.648829	25.2	-359.1
XIVa (R=Me)	-1834.480459	0	-1834.617858	0	
$TS_{XIVa\ (1)}$ (R=Me)	-1834.436391	27.6	-1834.571636	29.0	-244.4
$TS_{XIVa-XXVIIa}$ (R=Me)	-1834.440021	25.4	-1834.574564	27.2	-367.0

a) Sum of electronic and thermal enthalpies in hartrees. In the case of solvent energies (dcm) it refers to E electronic energies b) Enthalpy in kcal/mol, relative to compounds **XIa**, **XVIII** or **XVIII'**. c) Sum of electronic and thermal Free Energies in hartrees. d) Free energy in kcal/mol, relative to compounds **XIa**, **XVIII** or **XVIII'**.

Table S2. Absolute and relative enthalpies (H) and free Gibbs energies (G) of stationary points for complementary Schemes 9 and 12 in the Supporting Information

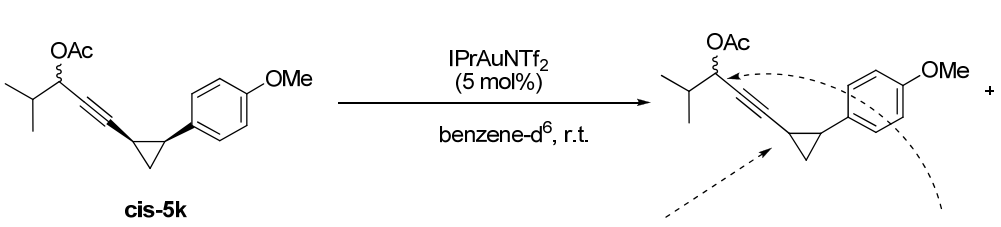
	Absolute enthalpy (H)[a]	Relative enthalpy (ΔH)[b]	Absolute Free energy (G)[c]	Relative Free energy (ΔG)[d]	Imaginary frequencies
XIVa	-1174.038448	-6.7	-1174.123853	-6.8	
dcmXIVa	-1174.455331	-5.1			
TS_{XIVa} (1)	-1174.007528	12.7	-1174.090987	13.8	-93.0
dcmTS_{XIVa}(1)	-1174.426689	12.9			
***ent*-TS_{XIVa} (1)**	-1173.994680	20.8	-1174.078343	21.7	-145.2
XVa	-1174.087856	-37.7	-1174.171878	-37.0	
dcmXVa	-1174.506704	-37.3			
***ent*-XVa**	-1174.088666	-38.2			
dcm$TS_{XIVa\text{-}XXVIIIa}$	-1174.418852	17.8			
dcmXXVIIIa	-1174.424125	14.5			
dcm$TS_{XXVIIIa\text{-}cisXIVa}$	-1174.421723	16.0			
dcm*cis*-XIVa	-1174.451036	-2.4			
dcm$TS_{cisXIVa}$(1)	-1174.426922	12.7			

a) Sum of electronic and thermal enthalpies in hartrees. In the case of solvent energies (dcm) it refers to E electronic energies. b) Enthalpy in kcal/mol, relative to compounds **XIa**. c) Sum of electronic and thermal Free Energies in hartrees. d) Free energy in kcal/mol, relative to compounds **XIa**.

7.5 List of coordinates

For list of coordinates see supporting information

8. Isomerization experiments for *cis*- and *trans*-5k



	trans/cis	% conv.	d.r.	% conv.
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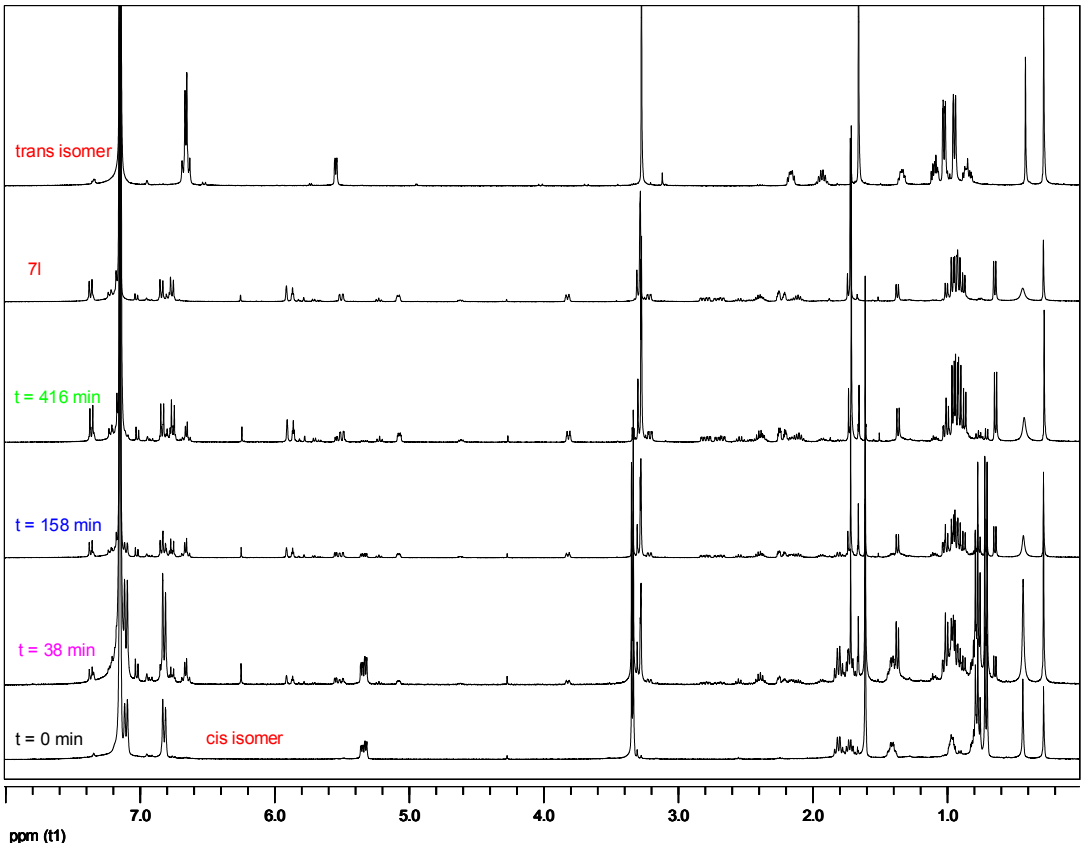
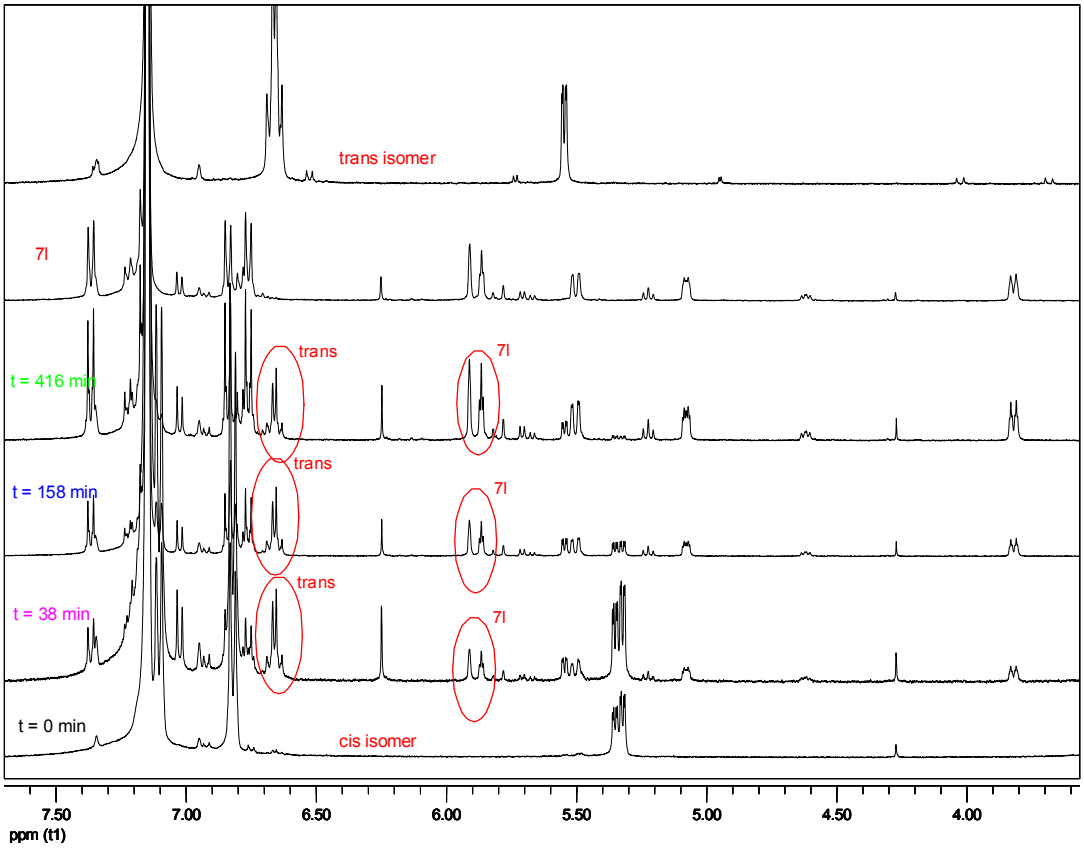
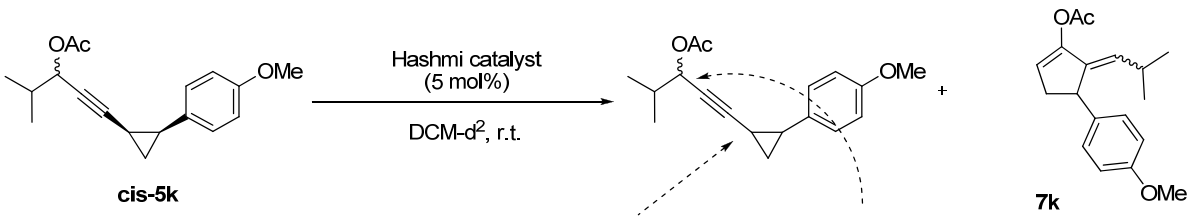
t = 21 min	0.09:1	83%	100:83	17%
t = 38 min	0.17:1	76%	100:83	23%
t = 88 min	0.37:1	58%	100:88	42%
t = 158 min	0.64:1	45%	100:100	55%
t = 196 min	0.88:1	38%	100:100	62%
t = 416 min	14:1	22%	100:100	78%
t = 486 min	16:1	15%	100:100	85%
t = 720 min	---	---	---	100%




trans isomer
7l
t = 416 min
trans
7l
t = 158 min
trans
7l
t = 38 min
trans
7l
t = 0 min
cis isomer
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
ppm (t1)



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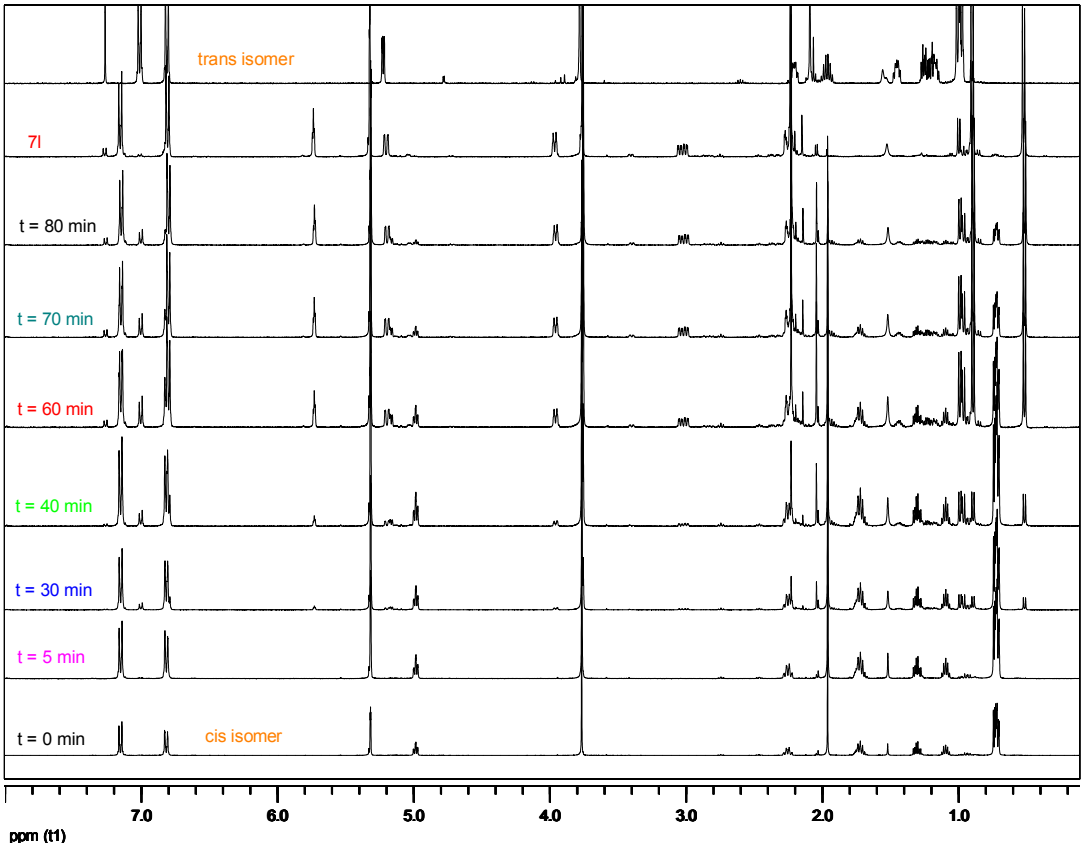
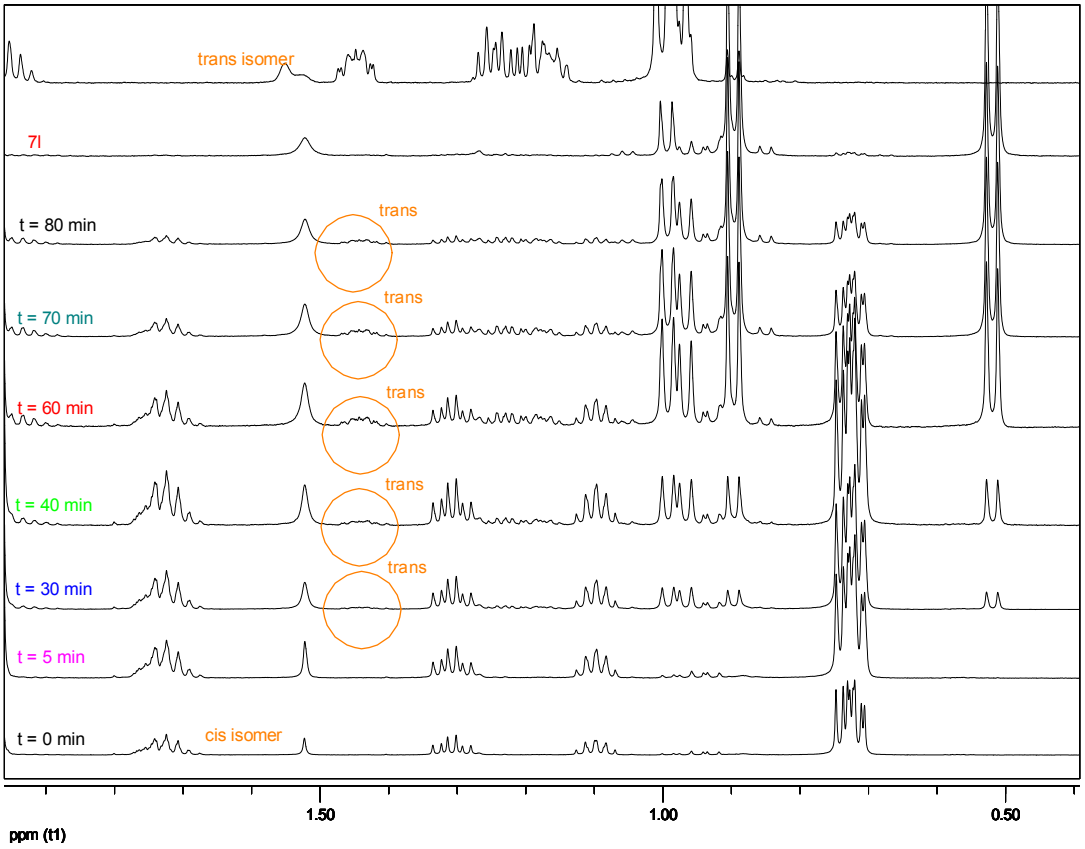
t = 30 min	1:5	88%	--	12%
t = 40 min	1:4	83%	--	17%
t = 60 min	1:2	59%	--	41%
t = 80 min	1.4:1	35%	--	65%

* The signals for the propargylic position overlaps. The diastereoisomeric ratio cannot be determined




trans isomer
7l
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trans
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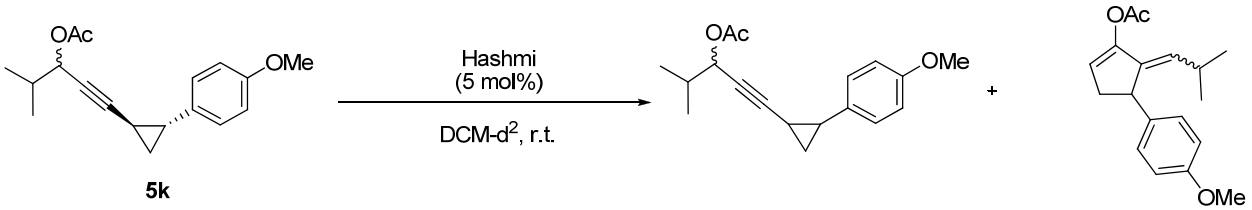
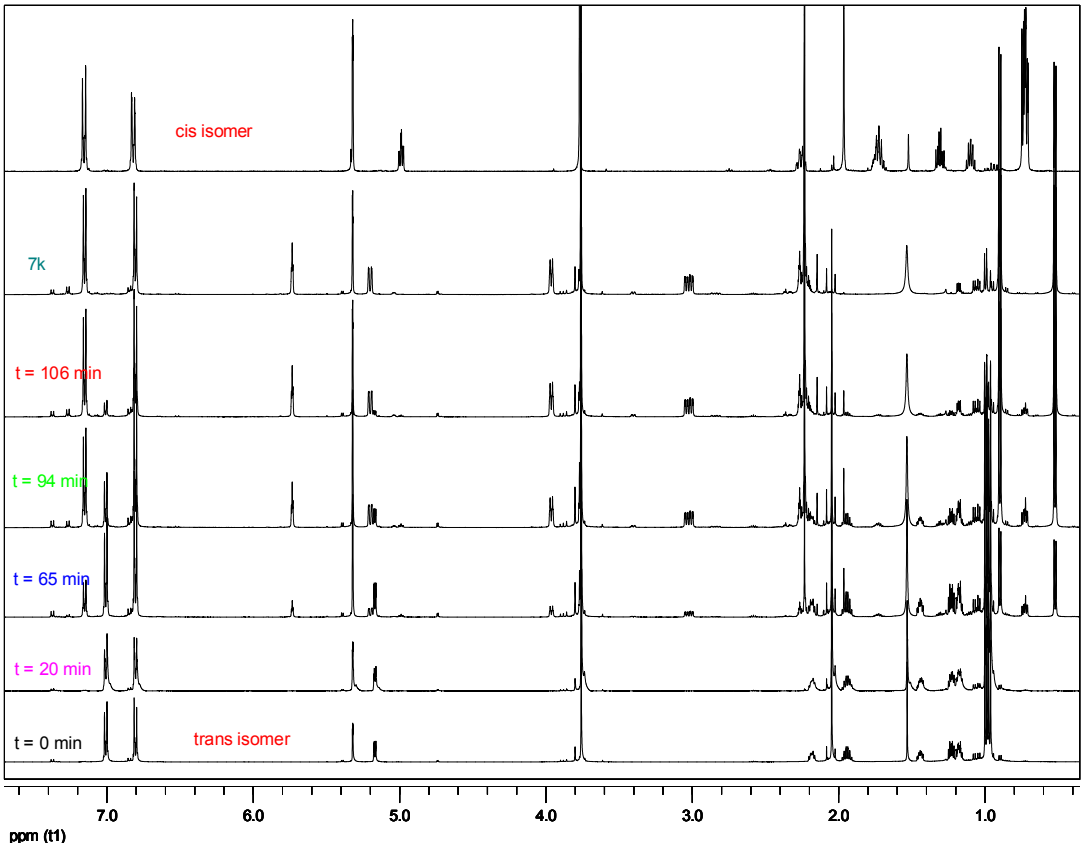
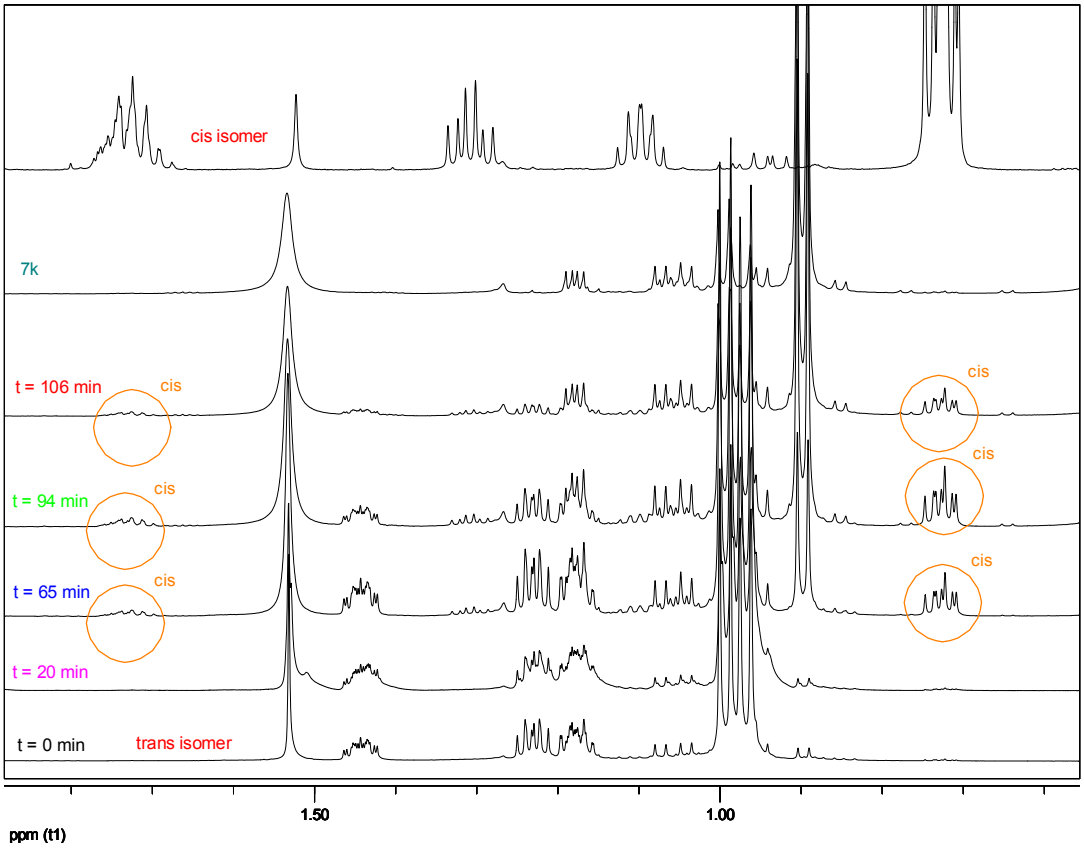
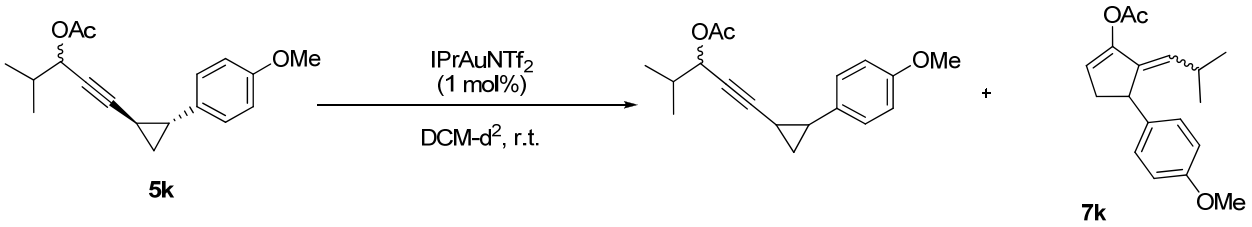
cis isomer
1.50
1.00
0.50
ppm (t1)



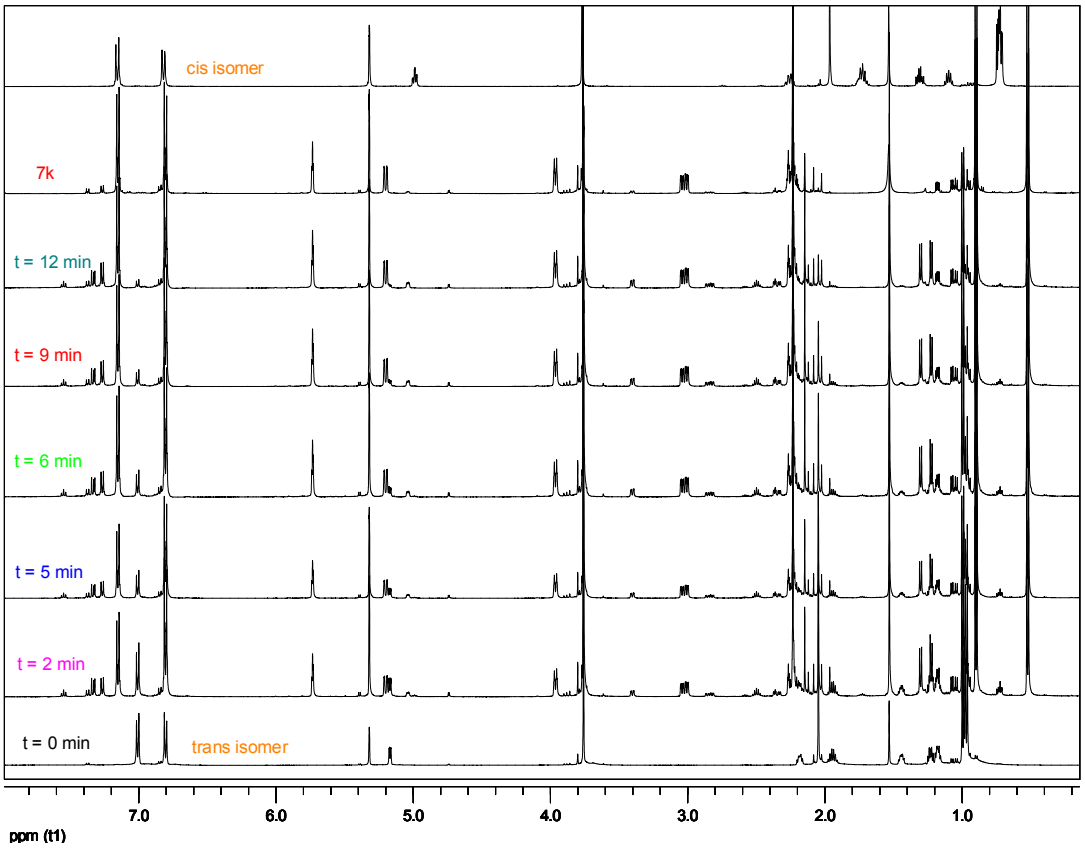
	trans/cis	% conv.	d.r.	7k % conv.
t = 0 min	100:0	100%	1:1	n.d.
t = 20 min	1:0.03	100%	1:1	0%
t = 65 min	1:0.14	72%	1:1	28%
t = 94 min	1:0.39	38%	1:1	62%
t = 106 min	1:0.41	17%	1:1	83%
t = 120 min	—	—	—	100%

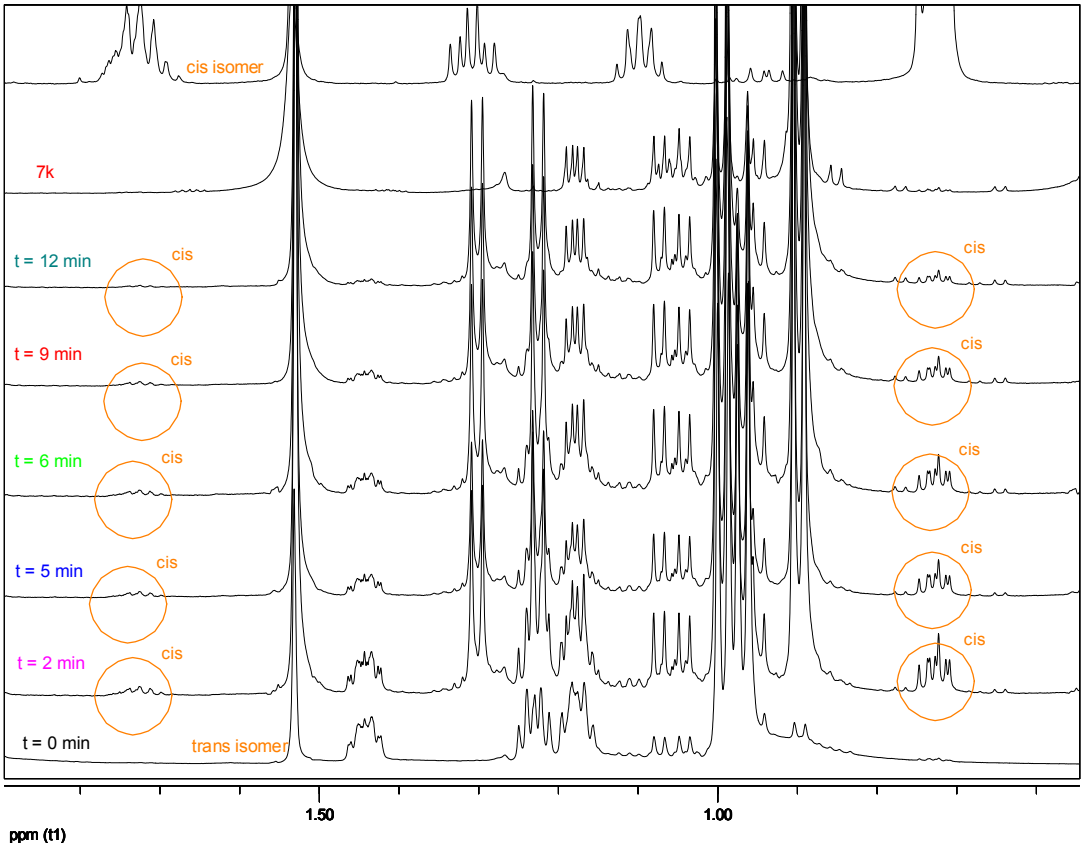



cis isomer
7k
t = 106 min
cis
t = 94 min
cis
t = 65 min
cis
t = 20 min
t = 0 min
trans isomer
cis
cis
cis
1.50
1.00
ppm (t1)



	trans/cis	% conv.	d.r.	% conv.
t = 0 min	100:0	100%	----	n.d.
t = 2 min	6:1	42%	----	58%
t = 5 min	6:1	27%	----	73%
t = 6 min	6:1	19%	----	81%
t = 9 min	10:1	12%	----	88%
t = 12 min	50:1	6%	----	94%
t = 15 min	----	----	----	100%




cis isomer
7k
t = 12 min
cis
t = 9 min
cis
t = 6 min
cis
t = 5 min
cis
t = 2 min
cis
t = 0 min
trans isomer
cis
cis
cis
cis
cis
1.50
1.00
ppm (t1)

Chapter 4

Gold-Catalyzed Cyclopenta/heptannulation Cascades: A Stereocontrolled Approach to the Scaffold of Frondosins A and B

CHAPTER 4

Gold-Catalyzed Cyclopenta/heptannulation Cascades: A Stereocontrolled Approach to the Scaffold of Frondosins A and B

D. Garayalde, K. Krüger and C. Nevado*

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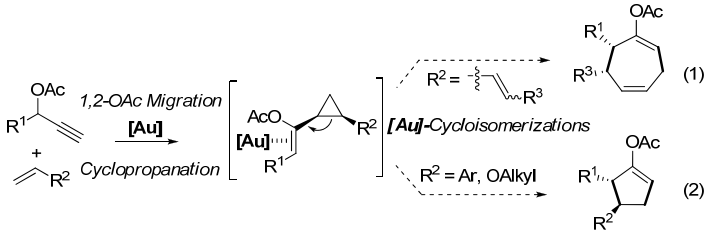
4.1 Introduction

Seven-membered ring carbocycles are ubiquitous motives in a wide variety of natural products including guanascaterpenes, colchicines, phorbols and frondosins among many others.[1] Since direct cyclizations have proved to be inefficient to construct this particular ring size, alternative strategies have been devised mainly focused on cycloaddition reactions.[2] Both, inter- and intramolecular Rh-mediated [5+2] cycloadditions between vinylcyclopropanes and unsaturated moieties have been successfully developed.[3] Another widespread method uses rhodium-vinyl carbenoids and dienes through formal [4+3] cycloadditions.[4] However, this methodology still presents several drawbacks: first, the metal carbenes are generated from the corresponding diazo compounds, which need to be pre-synthesized adding extra steps to the overall process and secondly, only donor-acceptor carbenoids provide high levels of selectivity. The development of versatile gold complexes in recent years has revealed gold catalysis as a powerful tool to build up molecular complexity.[5] As a representative example, the gold-catalyzed 1,2-acyloxy migration of propargyl esters generates a gold carbene, which can undergo a broad palette of transformations such as nucleophilic attack,[6] annulation,[7] subsequent acyloxy rearrangement[8] or olefin cyclopropanation.[9] Recently, gold-catalyzed ring expansions of stabilized cyclopropyl rings have also been reported.[10] We envisioned that a reaction sequence involving propargyl esters and dienes could be orchestrated in which gold not only catalyzed the 1,2-acetoxy migration and subsequent cyclopropanation, but could also re-activate the *in situ* generated vinyl acetate triggering a formal "Homo-Cope" rearrangement to give 7-membered rings in a highly straightforward manner (eq. 1).[11]

Furthermore, if alkenes instead of dienes were used, upon cyclopropyl ring opening highly substituted cyclopentenyl acetates could be obtained (eq. 2). Herein, we report the realization of these concepts and an application in a formal enantioselective synthesis of marine secondary metabolites Frondosins A and B.

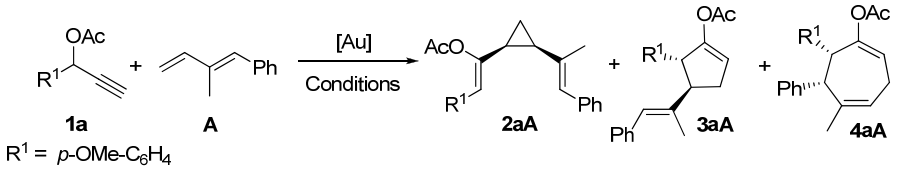
Scheme 1. Design of a Gold-Catalyzed 1,2-Acyloxy-Rearrangement/Cyclopropanation/ Cycloisomerization Cascades



4.2 Results and discussion

The reaction of *p*-methoxyphenylpropargyl acetate (**1a**) and (*E*)-(2-methylbuta-1,3-dienyl)benzene (**A**) in the presence of $IPrAuNTf_2$ cleanly delivered cyclopropane **2aA** and cycloheptenylacetate **4aA** in a 1:2 ratio (Table 1, entry 1). In the presence of a more electrophilic phosphite ligand, 5- and 7-membered rings **3aA** and **4aA** could be detected (Table 1, entry 2). Tris-(2,4-di-*tert*butylphenyl)phosphite-gold complex afforded similar results upon heating to 80ºC (Conditions I, entry 3), whereas $Ph_3PAuSbF_6$, provided a mixture of cyclopropyl **2aA** and 7-membered ring **4aA** in a 1:2 ratio (Table 1, entry 4). A combination of 2.5% $IPrAuNTf_2$ followed by 2.5% $(PhO)_3PAuSbF_6$ delivered **4aA** in 69% yield (Conditions II, entry 5). Finally, [(2-biphenyl)di-*tert*butylphosphine]-gold complex selectively afforded **4aA** in 85% yield providing the optimal reaction conditions (Conditions III, entry 6).

Table 1. Reaction Optimization[a]

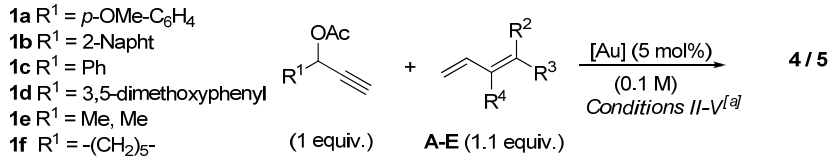


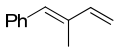
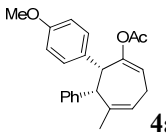
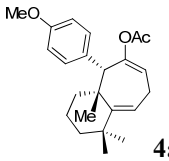
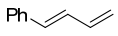
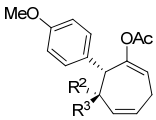
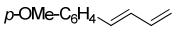
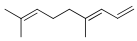
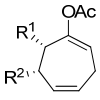
Entry	[Au]/Solvent/Time[a]	Con.	Ratio[b] [**2**/**3**/**4**]**aA**
1	$IPrAuNTf_2$, DCM, 30 min.	-	1/0/2
2	$(PhO)_3PAuSbF_6$, DCM, 30 min.	-	0/1/5
3	$[(2,4\text{-di-}t\text{Bu-}C_6H_3O)_3P]AuSbF_6$, 1,2-DCE, 80 ºC, 30 min.	I	0/1/3
4	$Ph_3PAuSbF_6$, DCM, 30 min.	-	1/0/2
5	$IPrAuNTf_2$ (2.5%), DCM, 10 min. then $(PhO)_3PAuSbF_6$ (2.5%), DCM, 30 min.	II	1/1/10 (69)
6	**[(2-Biphenyl)di-*t*Bu-phosphine]$AuSbF_6$, DCM, 30 min.**	**III**	**0/0/1 (85)**

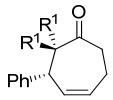
[a] Reaction Conditions: **1a** (1 equiv.), **A** (1.1 equiv.), [Au] (5 mol%), T= 25ºC, concentration: 0.1 M. [b] Determined by ^{1}H-NMR (isolated yield).

We then set out to explore the scope of this gold-catalyzed intermolecular cycloheptannulation (Table 2). Using **1a** as benchmark substrate we evaluated the influence of the dienic counterpart in the reaction. Congested alkenes reacted efficiently providing access to complex bicyclic scaffolds such as **4aB** (Table 2, entry 2), whereas more reactive monosubstituted dienes such as **C** and **D** partially polymerized under these conditions. The bi-catalytic system (Conditions II, Table 1) proved to be highly efficient for this type of substrates affording the corresponding cycloheptenylacetates **4aC-D** in high yields (Table 2, entries 3 and 4). Geranyl derivative **E** reacted with **1a** upon heating to give **4aE** in moderate yield (Table 2, entry 5). Acetates bearing 2-naphthyl-, phenyl- and 3,5-dimethoxyphenyl substitutents in the propargylic position (**1b-d**) reacted smoothly under conditions II to give the corresponding 7-membered rings **4(b-d)C/D** (Table 2, entries 6-11). 1,1-Dialkylsubstituted propargyl acetates **1e** and **1f** could also be transformed into the corresponding cycloheptenones **5eC** and **5fC** upon hydrolysis of the reaction mixture under basic conditions (Table 2, entries 12 and 13). This cycloheptannulation process is highly stereoselective, affording only *cis*-cycloheptenylacetates as major products.[12,13]

Table 2. Au-Catalyzed Cycloheptannulation: Reaction Scope



Entry	Dienes	Product [**4**/**5**]	Cond.[a] Yield [b] (%)
1	**1a**	 **A**  **4aA**	III, 85
2	**1a**	 **B**  **4aB**	III, 59
3	**1a**	 **C**  **4aC** (R^2 = Ph, R^3=H)	II, 92
4	**1a**	 **D**	**4aD** R^2 = *p*-OMe-C_6H_4, R^3=H	II, 77
5	**1a**	 **E**	**4aE** R^2 = -$(CH_2)_2$-CH=C$(Me)_2$, R^3 = Me	IV, 37
6	**1b**	**C**  **4bC** R^1 = 2-Napht, R^2 = Ph	II, 72
7	**1b**	**D**	**4bD** R^1= 2-Napht, R^2 = *p*-OMe-C_6H_4-	II, 55
8	**1c**	**C**	**4cC** R^1 = Ph, R^2 = Ph	II, 80

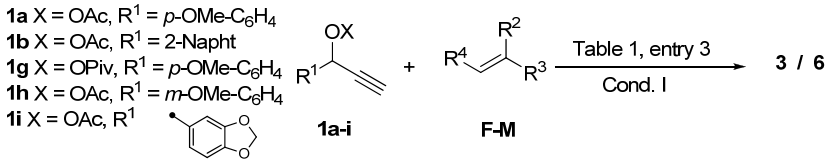
9	**1c**	**D**	**4cD** R^1 = Ph,R^2 = *p*-OMe-C_6H_4	II, 50
10	**1d**	**C**	**4dC** R^1= 3,5-dimethoxyphenyl, R_2 = Ph	II, 74
11	**1d**	**D**	**4dD** R^1=3,5-dimethoxyphenyl, R^2 = *p*-OMe-C_6H_4	II, 44
12	**1e**	**C**	 **5eC** R^1 = Me	V, 52
13	**1f**	**C**	**5fC** R^1 = -$(CH_2)_5$-	V, 79

[a] Conditions II and III from Table 1. Cond. IV: As III but heating to 120 ºC in 1,2-DCE; Cond. V: As IV followed by K_2CO_3/MeOH. [b] Isolated yields.

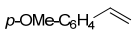
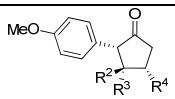
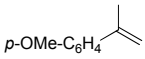
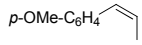
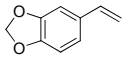
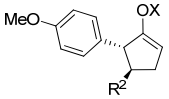
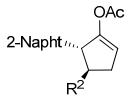
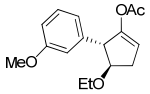
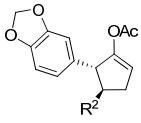
The chemoselectivity of the reaction is also remarkable, as neither cyclopropane intermediates (**2**)[14] nor products of a competitive intramolecular hydroarylation could be detected under these conditions.[15]

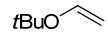
We hypothesized that alkenes could also participate in this gold-catalyzed cascade (Table 3). The reaction of **1a** with 4-methoxystyrene (**F**) (1 equiv.) in the presence of tris-(2,4-di-*tert*butylphenyl)phosphite-gold complex under conditions I proved to be extremely efficient affording cyclopentenone **6aF** in 90% yield. **6aF** is formed upon in situ hydrolysis of the corresponding cyclopentenylacetate under the reaction conditions (Table 3, entry 1).[16] Different substitution patterns in the olefinic counterpart were then examined. 1-Methoxy-4-(prop-1-en-2-yl)benzene (**G**), (*Z*)-1-methoxy-4-(prop-1-enyl)benzene (**H**) and 5-vinylbenzo-[*d*]-[1,3]-dioxole (**I**) reacted with **1a** affording ketones **6aG-I** in good yields (Table 3, entries 2-4). Alcoxy vinyl ethers (**J**-**K**) reacted smoothly with **1a** at room temperature furnishing the corresponding cyclopentenyl acetates **3aJ-K** (Table 3, entries 5 and 6). A bulkier pivaloyl ester (**1g**) was also tolerated affording **3gJ** in 82% yield (Table 3, entry 7). Comparable results were also obtained for 2-naphthyl (**1b**), 3-methoxyphenyl (**1h**) and benzo-[*d*]-1,3-dioxole (**1i**) substituted propargyl acetates as shown in entries 8 to 14 of Table 3. The reaction is also highly diastereoselective since, in most cases, only *trans*-2,3-disubstituted cyclopentenyl derivatives were observed.[12]

Table 3. Au-Catalyzed Cyclopentannulation: Reaction Scope



Entry	Olefin	Product [**3**/**6**]	Yield [a](%)

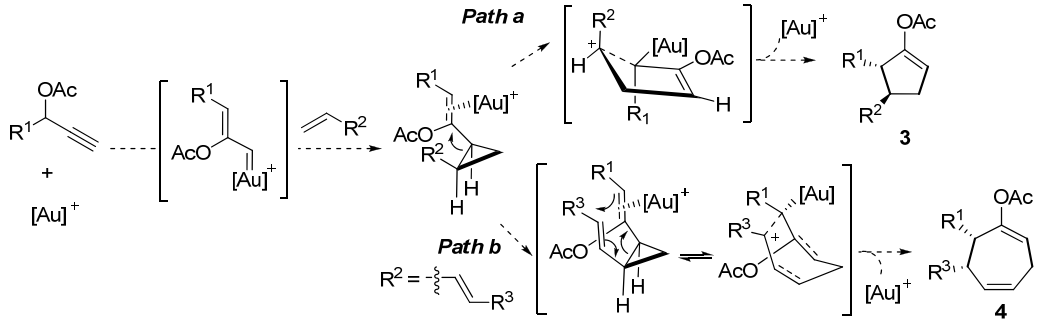
1	**1a**	 **F**	 **6aF** (R^2= *p*-OMe-C_6H_4, R^3= R^4=H)	90
2	**1a**	 **G**	**6aG** (R^2= *p*-OMe-C_6H_4, R^3= Me, R^4=H)	82[b]
3	**1a**	 **H**	**6aH** (R^2= *p*-OMeC_6H_4, R^3= H, R^4= Me)	78
4	**1a**	 **I**	**6aI** (R_2 =  , R_3=R_4=H)	63
5	**1a**	 **J**	 **3aJ** (X = OAc, R^2 = OBn)	83[c]
6	**1a**	 **K**	**3aK** (X = OAc, R^2 = OEt)	75[c,d]
7	**1g**	**J**	**3gJ** (X = OPiv, R^2 = OBn)	82[c]
8	**1b**	**J**	 **3bJ** (R^2 = OBn)	79[c]
9	**1b**	**K**	**3bK** (R^2 = OEt)	73[c,d]
10	**1h**	**K**	 **3hK**	60[c,d]
11	**1i**	**J**	 **3iJ** (R^2 = OBn)	87[c]
12	**1i**	**K**	**3iK** (R^2 = OEt)	87[c,d]
13	**1i**	 **L**	**3iL** (R^2 = OBu)	59[c]

14	**1i**	 **M**	**3iM** ($R^2 = O^tBu$)	87[c,d]

[a] Isolated yields of compounds obtained as single diastereoisomers unless otherwise stated. [b] Upon hydrolysis of the crude mixture with K_2CO_3 (2 equiv.), MeOH, rt, 30 min (d.r. 7:1). rt, 1 h. [c] Reaction at room temperature. [d] Olefin (5 equiv.).

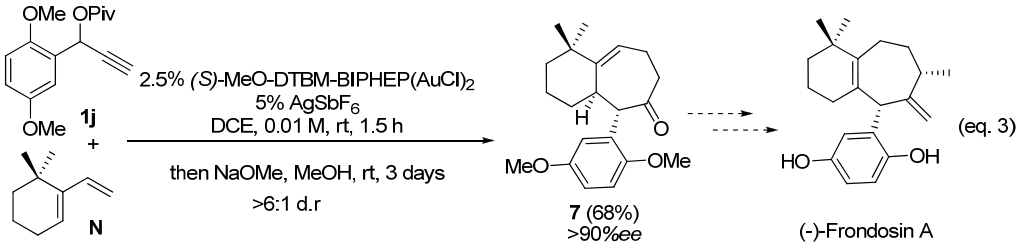
A possible mechanism for these transformations is shown in Scheme 2. The gold-mediated isomerization of the propargyl ester leads to Au-carbene, which reacts with the olefinic counterpart to form a *cis*-cyclopropane intermediate.[9] Subsequent gold re-activation of the vinyl acetate moiety triggers the cyclopropyl ring opening provided stabilization of the *in situ* generated δ^+ is present, forming a 1,5-dipole.[10] An envelope conformation is proposed for the transition state with substituents disposed in a *trans-pseudo*diaxial fashion to minimize torsional/steric interactions yielding *trans*-2,3-disubstituted cyclopentannulation products **3 (**Path a).[17] In contrast, when 1,4-dienes were used, the cyclopropyl system undergoes a Au-catalyzed Cope rearrangement delivering *cis*-2,3-disubstituted cycloheptenyl acetates **4 (**Path b).[11] A boat-like transition state is proposed in this case to account for the observed *cis*-relative stereochemistry.

Scheme 2. Mechanistic Proposal



To capitalize on the structural complexity built up in the formal Au- catalyzed [4+3] cycloaddition, we envisioned a synthetic application towards the core of Frondosins, marine norsesquiterpenoids with promising biological activities, particularly Frondosin A, the most potent member of the series.[18] Several approaches towards the core of Frondosins have been disclosed but only one enantioselective synthesis of (+)-Frondosin A has been reported so far.[19] Treatment of acetate **1j** and 6,6-dimethyl-1-vinyl cyclohexene (**N**) with (*S*)-OMe-DTBM-BIPHEP-gold(I) complex afforded, quantitatively, the corresponding bicyclic cycloheptenyl pivaloate. In situ hydrolysis and subsequent equilibration with NaOMe/MeOH yielded thermodynamically favored ketone **7** in 68% yield and >90% *ee* (eq. 3).[12] Since this bicyclic enone has been recently elaborated to Frondosins A and B,[20] our approach represents a streamlined formal enantioselective synthesis of both molecules.

Scheme 3. Formal Total Synthesis of Frondosins A and B



4.3 Conclusion

In summary, we report here two highly diastereoselective, gold-catalyzed 3-steps-cascade processes for the synthesis of highly substituted five and seven-membered rings from propargyl acetates and alkenes or 1,4-dienes, respectively. The reaction favors *trans*-2,3-disubstituted cyclopentenylacetates through a tightly bound carbocationic transition state whereas the gold-catalyzed Cope rearrangement delivers *cis*-2,3-disubstituted cyclopheptenylacetates. This gold-catalyzed formal [4+3] cycloaddition represents an attractive alternative to previously reported Rh-catalyzed methodology both in terms of atom-economy and functional group tolerance. In addition, the concerted nature of the process has allowed an alternative, formal enantioselective synthesis of both Frondosins A and B.

4.4 References

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[12] See Supporting Information for additional details.

[13] Treatment of the reaction mixtures in Table 2 with K_2CO_3/MeOH afforded the thermodynamically favored *trans*-2,3-disubstituted cycloheptenones (**5**) quantitatively. Cycloheptenylacetates (**4**) are thus formed under kinetic control. See Supporting Information.

[14] The gold-free, thermal Cope-rearrangement of several cyclopropyl intermediates (**2aA-C**) failed even at temperatures up to 80 ºC. Cyclopropyl **2aB** is transformed into the corresponding cycloheptenyl acetate **4aB** upon treatment with [(2-biphenyl)di-*tert*butylphosphine]-gold complex . See Supporting Information.

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[16] Under the conditions I (Table 1, entry 3), **2aA** and **3aA** could be independently transformed into **6aA**, meaning that under these conditions, cyclopropanes **2** are direct precursors of the 5-membered rings. See Supporting Information.

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Chapter 4

Experimental Section

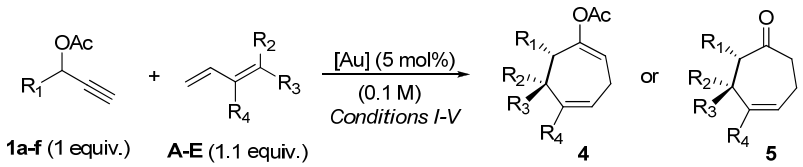
Contents:

1. General information

All reactions were carried under non-inert atmosphere. All reagents were used as received unless otherwise noted. Solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). The olefins **C**, **F**, **K**, **L**, and **M** are commercially available by Aldrich. The following compounds were prepared according to previously reported procedures: (**1a**, **1b**, **1c**)[1]; **1e**[2]; **1f**[3]; **1g**[4]; (**1i**, **1h**, **1d**)[5]; **A**[6]; **B**[7]; **D**[8]; **E**[9]; **G**[10]; **H**[11]; **I**[12]; **J**[13]; **N**[14]. Reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silacycle silica gel (230-400 mesh). NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual 1H and 13C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), doublet-doublet-doublet (ddd), quintet (quint), septet (sept), multiplet (m), and broad (br). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer 10 spectra were acquired. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 <l PEG200, 2 <l PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100ml MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard. HPLC was performed on Jasco PU-2089 plus instrument using a MD-2018 plus photodiode array detector and 0.46 x 25 cm Chiralcel OD-H columns (hexane/isopropanol). $[\alpha]_D$ value was recorded on JASCO P-2000 Polarimeter at 25 ^oC.

2. Experimental Procedures

All reactions were run between 0.1 and 0.5 mmol scale.



I. To a solution of the corresponding propargyl acetate (1.0 equiv.) and diene (1.1 equiv.) in 1,2-DCE (0.1 M), (1,4-di-*t*Bu-$C_6H_3O)_3PAuSbF_6$ (0.05 equiv.) was added. The mixture was stirred at 80 ^0C for 30 minutes. The reaction was quenched with triethylamine (0.05 equiv.). The solvent was removed under reduce pressure giving the corresponding cyclopenten- and cycloheptenylacetates in 1:3 ratio.

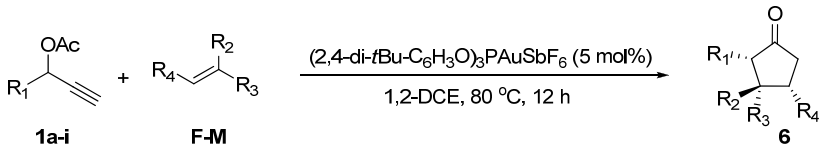
II. To a solution of the corresponding propargyl acetate (1.0 equiv.) and diene (1.1 equiv.) in DCM (0.1 M), $IPrAuNTf_2$ (0.025 equiv.) was added. The mixture was stirred at room temperature for 10 minutes. Then $(PhO)_3PAuSbF_6$ (0.025 equiv.) was added and the mixture was stirred at room temperature for 30 minutes. The reaction was quenched with triethylamine (0.05 equiv.) and the solvent was removed under reduce pressure. The residue was purified by column chromatography (Hex:AcOEt) to give the corresponding cycloheptenylacetates in 44-92% yield.

III. To a solution of the corresponding propargyl acetate (1.0 equiv.) and diene (1.1 equiv.) in DCM (0.1 M), [(2-biphenyl)-di-*tert*-butyl-phosphine]$AuSbF_6$ (0.05 equiv.) was added. The mixture was stirred at room temperature for 30 minutes. The reaction was quenched with triethylamine (0.05 equiv. The solvent was removed under reduce pressure. The residue was purified by column chromatography (Hex:AcOEt) to give the corresponding cycloheptenylacetate in 59-85% yield.

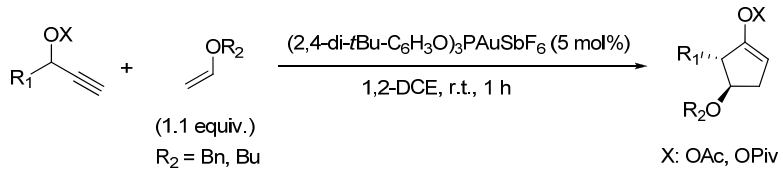
IV. To a solution of the corresponding propargyl acetate (1.0 equiv.) and the corresponding diene (1.1 equiv.) in 1,2-DCE (0.1 M), [(2-biphenyl)-di-*tert*-butyl-phosphine]$AuSbF_6$ (0.05 equiv.) was added. The mixture was stirred at room temperature for 30 minutes and the mixture was stirred at 120 ^oC for 12 hours. The solvent was removed under reduce pressure. The residue was purified by column chromatography (Hex:AcOEt) to give the corresponding cycloheptenylacetate in 37% yield.

V. To a solution of the corresponding propargyl acetate (1.0 equiv.) and the corresponding diene (1.1 equiv.) in 1,2-DCE (0.1 M), [(2-biphenyl)-di-*tert*-butyl-phosphine]$AuSbF_6$ (0.05 equiv.) was added. The mixture was stirred at room temperature for 30 minutes and the mixture was stirred at 120 ^oC for 12 hours. The solvent was removed under reduce pressure. Then K_2CO_3 (2 equiv.) and methanol were added and the mixture was stirred at room temperature for 30 minutes. The mixture was filtrated over Celite®. The solvent was removed under reduce pressure. The residue was purified by column chromatography (Hex:AcOEt) to give the corresponding cyclohept-4-enones in 52-79% yield.

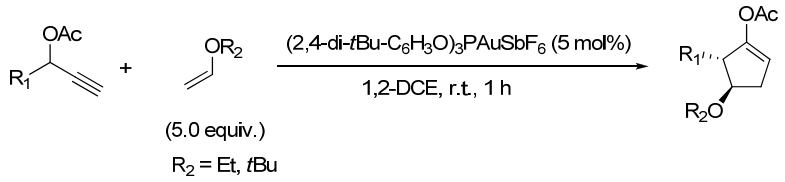
For 5-membered rings:



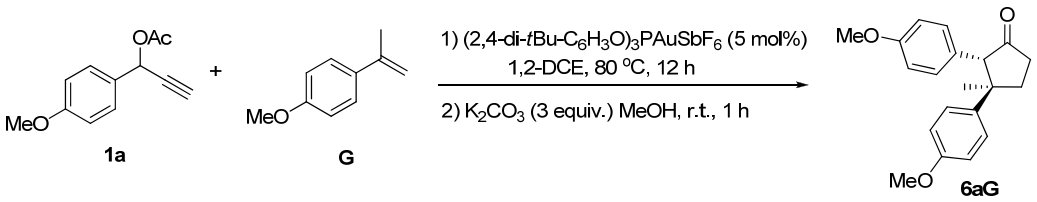
To a solution of the corresponding propargyl acetate (1.0 equiv.) and the corresponding olefin (1.1 equiv.) in 1,2-DCE (0.1M), (1,4-di-*t*Bu-$C_6H_3O)_3PAuSbF_6$ (0.05 equiv.) was added. The mixture was stirred at 80 ^oC for 12 hours. The reaction was quenched with triethylamine (0.05 equiv.). The solvent was evaporated under reduce pressure and the residue was purified by column chromatography (Hex:AcOEt) to give the corresponding cyclopentanones in 56-90% yield.



To a solution of the corresponding propargyl ester (1.0 equiv.) and the corresponding olefin (1.1 equiv.) in 1,2-DCE (0.1 M), (1,4-di-*t*Bu-$C_6H_3O)_3PAuSbF_6$ (0.05 equiv.) was added. The mixture was stirred at room temperature for 1 hour. The reaction was quenched with triethylamine (0.05 equiv.). The solvent was evaporated under reduce pressure and the residue was purified by column chromatography (gradient Hex:AcOEt) to give the corresponding cyclopent-1-enyl esters in 59-87% yield.



To a solution of the corresponding propargyl acetate (1.0 equiv.) and ethyl vinyl ether (5.0 equiv.) in 1,2-DCE (0.1M), (1,4-di-*t*Bu-$C_6H_3O)_3PAuSbF_6$ (0.05 equiv.) was added. The mixture was stirred at room temperature for 1 hour. The reaction was quenched with triethylamine (0.05 equiv.). The solvent was evaporated under reduce pressure and the residue was purified by column chromatography (Hex:AcOEt 8:1) to give the corresponding cyclopent-1-enyl acetates in 60-87% yield.

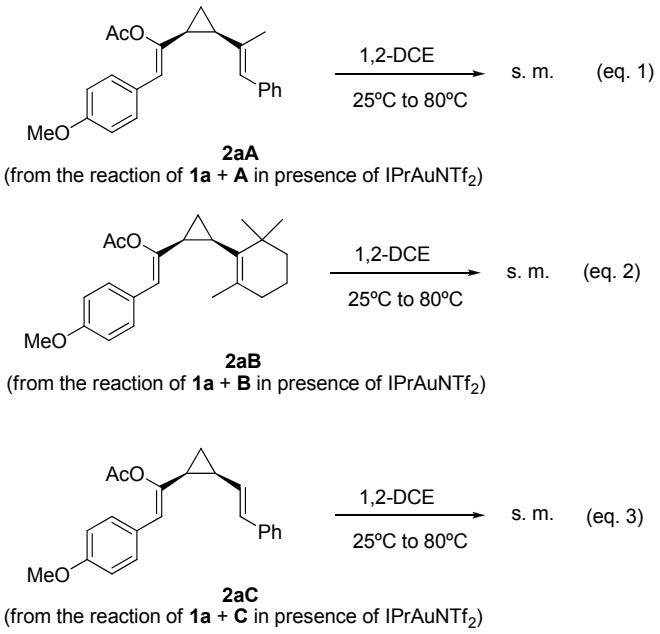


To a solution of propargyl acetate **1a** (0.060 mmol, 1.0 equiv.) and olefin **G** (0.066 mmol, 1.1 equiv.) in 1,2-DCE (1.18 mL, 0.1M), (2,4-di-*t*Bu-$C_6H_3O)_3PAuSbF_6$ (0.003 mmol, 0.05 equiv.) was added. The mixture was stirred at 80 °C for 12 hours. The reaction was quenched with triethylamine (0.05 equiv.). The solvent was evaporated under reduce pressure. Then K_2CO_3 and methanol were added and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with brine and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduce pressure. The residue was purified by column chromatography (Hex: AcOEt 10:1) to give the corresponding cyclopentanone **6aG** (15 mg) in 82% yield.

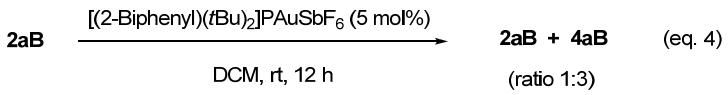
3. Additional Experiments (Ref. 13, 14, 16)

Ref. 14

Equations 1, 2 and 3 confirm that cyclopropane intermediates (**2**) are not transformed into the corresponding 7-membered rings in the absence of gold-catalyst, thus ruling out a metal-free Cope rearrangement pathway.

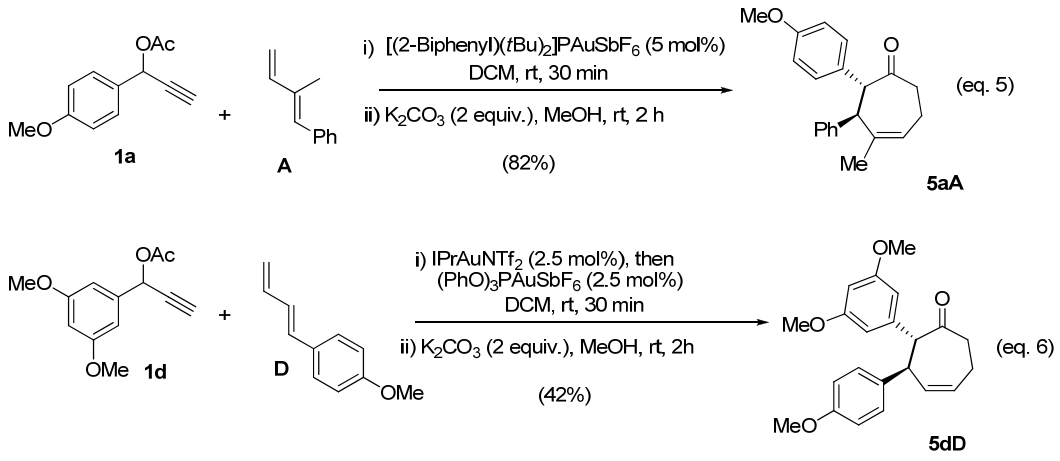


Cyclopropyl **2aB** can be transformed into cyclopentenylacetate **4aB** upon stirring in the presence of [(2-Biphenyl)(*t*Bu)$_2$]PAuSbF$_6$ (eq. 4).



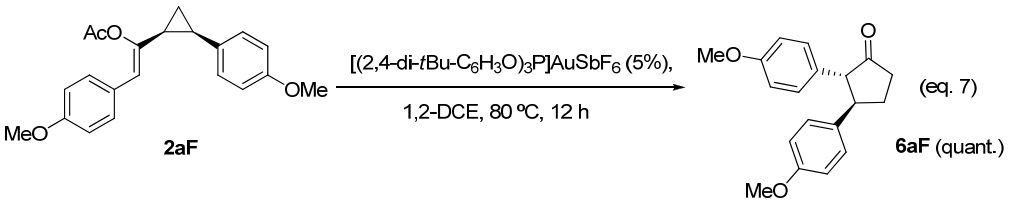
Ref. 13

Equations 5 and 6 are representative of a one-pot procedure for the hydrolysis of the "in situ" generated *cis*-disubstituted cycloheptenyl acetates (**4**) to the corresponding *trans*-cycloheptenones (**5**).

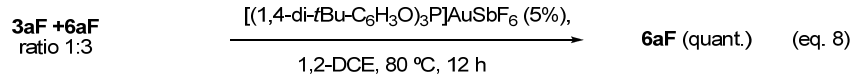


Ref. 16

To confirm that *cis*-cyclopropanes are the actual intermediates in the gold-catalyzed cyclopentannulation, cyclopropane **2aF** was submitted to the standard reaction conditions affording cyclopentanone **6aF** (Equation 7).

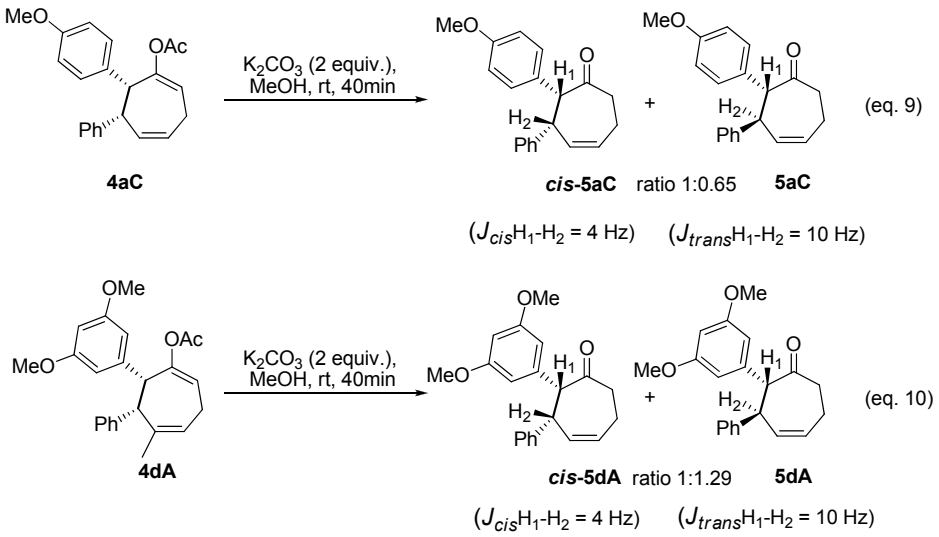


A mixture of cyclopentylacetate **3aF** and cyclopentanone **6aF** (1:3) was transformed into **6aF** under the standard reaction conditions confirming that the observed 5-membered ring ketones (**6**) were produced by hydrolysis of the corresponding cyclopentenyl acetates (**3**) under the reaction conditions.

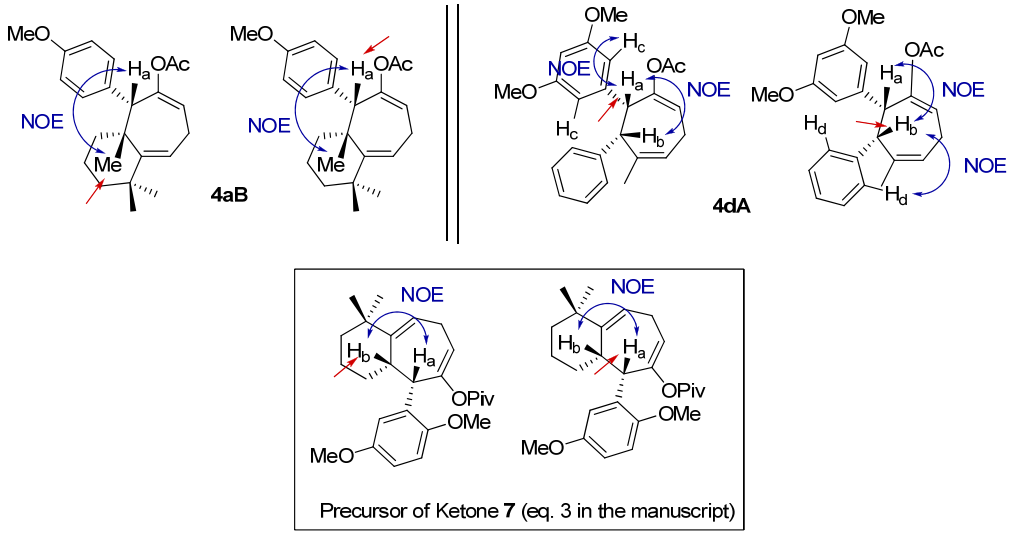


Assignment of the Relative Stereochemistry for compounds 4-5

When acetate **4aC** was hydrolyzed to the corresponding ketone with K_2CO_3/MeOH over 2 hours, **5aC** was the only product detected in the reaction mixture. Based on the value of the J^3 coupling constant between H_1 and H_2 (JH_1-H_2 = 10 Hz) we assumed a *trans*-relative configuration for cyclopentenone **5aC** (confirmed by X-Ray diffraction of **5aA** (JH_1-H_2 = 10 Hz), see forthcoming section 4 in this SI). However, when the hydrolysis reaction was stopped after only 40 min, the formation of two different ketones was observed: **5aC** but also ***cis*-5aC** (JH_1-H_2 = 4 Hz) was present in the mixture (eq. 9). This result indicates that the relative stereochemistry in the starting cyclopentenyl acetates is *"cis"* and, as a result of the direct hydrolysis of **4aC**, ***cis*-5aC** is detected after short reaction times, whereas **5aC** is obtained as a result of the hydrolysis + equilibration to the thermodynamically favored *trans*-2,3-disubstituted product. A similar outcome was observed for acetate **4dA** (eq. 10).



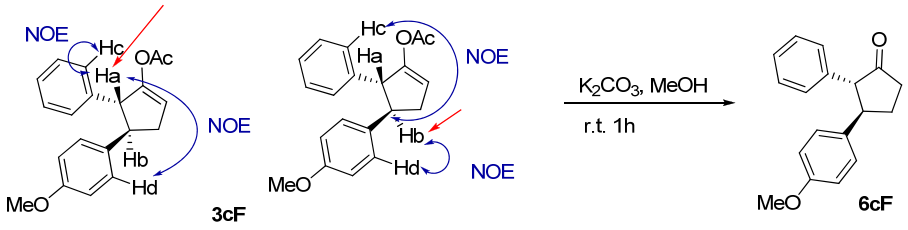
In addition, NOE-experiments were performed on key cycloheptenyl acetates to confirm the *cis*-relative stereochemistry of products **4** (Scheme 1). All traces of NOE-experiments can be found in Section 9 of this SI.



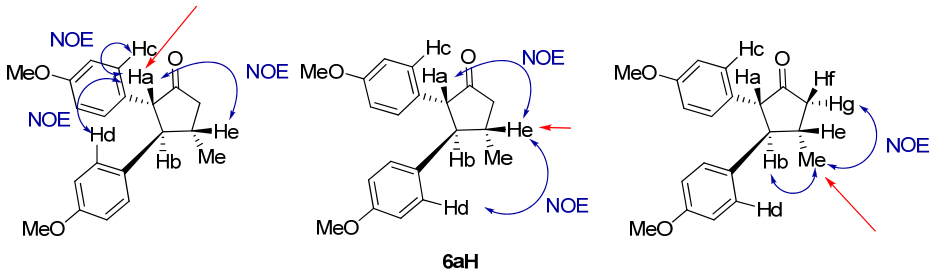
(Scheme 1)

Assignment of the Relative Stereochemistry for compounds 3-6

One of the few examples where two isomers were observed in the cyclopentannulation reaction was compound **3cF** which was obtained in a 3:1 diastereomeric ratio. The NOE studies confirmed the *"trans"* relationship between the two aromatic substituents in the major isomer (Scheme 2). Upon hydrolysis of this mixture with K_2CO_3/MeOH only one compound was obtained (**6cF**), which was assigned to the thermodynamically more stable *trans*-2,3-disubstituted cyclopentanone.



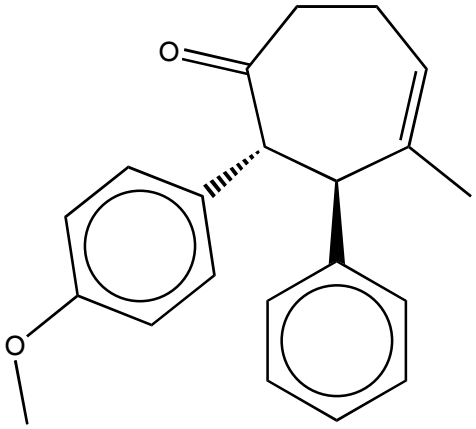
In accordance with the previous result, the hydrolysis of cyclopentenyl acetates **3aF**, **3aH** and **3aI** (single diastereoisomers) with K_2CO_3/MeOH gave the corresponding *"trans"* ketones **6aF**, **6aH** and **6aI**. Analysis of the hydrolysis mixtures at shorter reaction times only showed the presence of the *"trans"* cyclopentenones, thus confirming that in this case, the starting cyclopentenyl acetates are the "*trans*"-2,3-disubstituted diastereoisomers. In addition NOE experiments also confirmed the 2,3-"*trans*" relative stereochemistry in ketone **6aH** (Scheme 3).



6aH

(Scheme 3)

4. X-Ray Structure of 5aA



List of Tables

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5. Torsional Angles
6. General Atomic Displacement Parameter Expressions, U^{ij}'s
7. Positional and Displacement Parameters for Hydrogen Atoms

Figure Captions

1. *ORTEP*[1] representation of the molecule (50% probability ellipsoids; H-atoms given arbitrary displacement parameters for clarity)

Definition of Terms

Function minimized: $\Sigma w(F_o^2 - F_c^2)^2$

where $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$ and $P = (F_o^2 + 2F_c^2)/3$

$$F_o^2 = S(C - RB)/Lp$$

and $$\sigma^2(F_o^2) = S^2(C + R^2B)/Lp^2$$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan time to background counting time

B = Total background count

Lp = Lorentz-polarization factor

R-factors: $R_{int} = \Sigma|<F_o^2> - F_o^2| / \Sigma F_o^2$ summed only over reflections for which more than one symmetry equivalent was measured.

$R(F) = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$ summed over all observed reflections.

$wR(F^2) = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$ summed over all reflections.

Standard deviation of an observation of unit weight (goodness of fit): $[\Sigma w(F_o^2 - F_c^2)^2 / (N_o - N_v)]^{1/2}$ where N_o = number of observations; N_v = number of variables.

NOTES

The structure of $C_{21}H_{22}O_2$ (NBC-NA-311) has been solved and refined successfully with no unusual features. Since the space group is centrosymmetric, the compound in the crystal is racemic. The phenyl substituents are *trans*-disposed.

EXPERIMENTAL

Crystal-Structure Determination. – A crystal of $C_{21}H_{22}O_2$, obtained from CH_2Cl_2 / pentane, was mounted on a glass fibre and used for a low-temperature X-ray structure determination. All measurements were made on a *Nonius KappaCCD* area-detector diffractometer[2] using graphite-monochromated Mo *K*α radiation (λ = 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The unit cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of 3352 reflections in the range $4° < 2\theta < 50°$. The mosaicity was 1.047(1)°. A total of 685 frames were collected using ϕ and ω scans with κ offsets, 26 seconds exposure time and a rotation angle of 0.6° per frame, and a crystal-detector distance of 36.7 mm.

Data reduction was performed with *HKL Denzo* and *Scalepack*[3]. The intensities were corrected for Lorentz and polarization effects, but not for absorption. The space group was uniquely determined by the systematic absences. Equivalent reflections were merged. The data collection and refinement parameters are given in *Table 1*. A view of the molecule is shown in the *Figure*.

The structure was solved by direct methods using *SHELXS97* [4], which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom ($1.5U_{eq}$ for the methyl groups). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_o^2 - F_c^2)^2$. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. Plots of $\Sigma w(F_o^2 - F_c^2)^2$ versus $F_c/F_c(\max)$ and resolution showed no unusual trends. A correction for secondary extinction was applied. Five reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement.

Neutral atom scattering factors for non-hydrogen atoms were taken from Maslen, Fox and O'Keefe[5a], and the scattering factors for H-atoms were taken from Stewart, Davidson and Simpson[6]. Anomalous dispersion effects were included in F_c[7]; the values for f' and f'' were those of Creagh and McAuley[5b]. The values of the mass attenuation coefficients are those of Creagh and Hubbel[5c]. The *SHELXL97* program[8] was used for all calculations.

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(5) a) E.N. Maslen, A.G. Fox, M.A. O'Keefe, in 'International Tables for Crystallography', Ed. A.J.C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, pp. 477-486; b) D.C. Creagh, W.J. McAuley, *ibid*. Table 4.2.6.8, pp. 219-222; c) D.C. Creagh, J.H. Hubbell, *ibid*. Table 4.2.4.3, pp. 200-206.

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(7) J.A. Ibers, W.C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781-782.

(8) G.M. Sheldrick, *SHELXL97*, *Acta Crystallogr., Sect A* **2008**, *64*, 112-122.

Table 1. *Crystallographic Data*

Crystallised from		CH_2Cl_2 / pentane
Empirical formula		$C_{21}H_{22}O_2$
Formula weight [g mol^{-1}]		306.40
Crystal colour, habit		colourless, prism
Crystal dimensions [mm]		0.20 × 0.20 × 0.25
Temperature [K]		160(1)
Crystal system		orthorhombic
Space group		*Pbca* (#61)
Z		8
Reflections for cell determination		3352
2θ range for cell determination [°]		4–50
Unit cell parameters	a [Å]	9.0944(3)
	b [Å]	15.1241(6)
	c [Å]	24.6533(9)
	α [°]	90
	β [°]	90
	γ [°]	90
	V [Å^3]	3390.9(2)
F(000)		1312
D_x [g cm^{-3}]		1.200
μ(Mo $K\alpha$) [mm^{-1}]		0.0754
Scan type		ϕ and ω
2θ(max) [°]		50
Total reflections measured		36262
Symmetry independent reflections		2973
R_{int}		0.112
Reflections with $I > 2\sigma(I)$		1910
Reflections used in refinement		2968
Parameters refined		211
Final $R(F)$ [$I > 2\sigma(I)$ reflections]		0.0564
$wR(F^2)$ (all data)		0.1374
Weights:	$w = [\sigma^2(F_o^2) + (0.0473P)^2 + 0.6876P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$	
Goodness of fit		1.136
Secondary extinction coefficient		0.0029(8)
Final Δ_{max}/σ		0.001

$\Delta\rho$ (max; min) [e Å^{-3}]	0.18; -0.20
$\sigma(d_{(C-C)})$ [Å]	0.003 – 0.004

TABLE 2. Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) with standard uncertainties in parentheses.

* U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

ATOM	x	y	z	U_{eq}*
O(1)	1.0955(2)	0.7621(1)	0.36004(6)	0.0506(5)
O(2)	0.9888(2)	0.8913(1)	0.59864(6)	0.0534(5)
C(1)	0.9665(2)	0.7467(1)	0.35171(9)	0.0399(6)
C(2)	0.8445(2)	0.7947(1)	0.38190(9)	0.0373(6)
C(3)	0.7984(2)	0.8783(1)	0.34881(9)	0.0376(6)
C(4)	0.7786(2)	0.8672(2)	0.28812(9)	0.0414(6)
C(5)	0.7644(2)	0.7917(2)	0.2614(1)	0.0475(6)
C(6)	0.7722(2)	0.6993(2)	0.2834(1)	0.0475(6)
C(7)	0.9210(2)	0.6797(2)	0.30976(9)	0.0466(6)
C(8)	0.8831(2)	0.8183(1)	0.43996(9)	0.0360(6)
C(9)	1.0029(2)	0.8724(1)	0.45257(9)	0.0385(6)
C(10)	1.0352(2)	0.8943(1)	0.50509(9)	0.0401(6)
C(11)	0.9474(2)	0.8646(1)	0.54732(9)	0.0402(6)
C(12)	0.8266(2)	0.8118(1)	0.53622(9)	0.0427(6)
C(13)	0.7972(2)	0.7894(1)	0.48262(9)	0.0413(6)
C(14)	0.8908(3)	0.8736(2)	0.64224(9)	0.0520(7)
C(15)	0.6607(2)	0.9189(1)	0.37434(9)	0.0387(6)
C(16)	0.6676(3)	0.9952(2)	0.40487(9)	0.0450(6)
C(17)	0.5422(3)	1.0282(2)	0.4300(1)	0.0551(7)
C(18)	0.4097(3)	0.9851(2)	0.4247(1)	0.0570(7)
C(19)	0.4021(3)	0.9103(2)	0.3934(1)	0.0616(8)
C(20)	0.5259(2)	0.8774(2)	0.3682(1)	0.0518(7)
C(21)	0.7714(3)	0.9544(2)	0.2582(1)	0.0638(8)

TABLE 3. Bond lengths (Å) with standard uncertainties in parentheses.

O(1)	-C(1)	1.214(2)	C(8)	-C(13)	1.381(3)
O(2)	-C(11)	1.381(3)	C(8)	-C(9)	1.398(3)
O(2)	-C(14)	1.422(3)	C(9)	-C(10)	1.369(3)
C(1)	-C(7)	1.506(3)	C(10)	-C(11)	1.387(3)
C(1)	-C(2)	1.520(3)	C(11)	-C(12)	1.385(3)
C(2)	-C(8)	1.517(3)	C(12)	-C(13)	1.390(3)
C(2)	-C(3)	1.563(3)	C(15)	-C(16)	1.380(3)
C(3)	-C(4)	1.516(3)	C(15)	-C(20)	1.385(3)
C(3)	-C(15)	1.530(3)	C(16)	-C(17)	1.390(3)
C(4)	-C(5)	1.326(3)	C(17)	-C(18)	1.377(4)
C(4)	-C(21)	1.512(3)	C(18)	-C(19)	1.371(3)
C(5)	-C(6)	1.501(3)	C(19)	-C(20)	1.379(3)
C(6)	-C(7)	1.530(3)			

TABLE 4. Bond angles (°) with standard uncertainties in parentheses.

C(11)	-O(2)	-C(14)	117.9(2)	C(13) -C(8)	-C(2) 120.9(2)
O(1)	-C(1)	-C(7)	120.7(2)	C(9) -C(8)	-C(2) 121.9(2)
O(1)	-C(1)	-C(2)	122.1(2)	C(10) -C(9)	-C(8) 121.3(2)
C(7)	-C(1)	-C(2)	117.2(2)	C(9) -C(10)	-C(11) 120.5(2)
C(8)	-C(2)	-C(1)	113.9(2)	O(2) -C(11)	-C(12) 124.5(2)
C(8)	-C(2)	-C(3)	111.3(2)	O(2) -C(11)	-C(10) 115.9(2)
C(1)	-C(2)	-C(3)	109.0(2)	C(12) -C(11)	-C(10) 119.7(2)
C(4)	-C(3)	-C(15)	110.7(2)	C(11) -C(12)	-C(13) 118.7(2)
C(4)	-C(3)	-C(2)	117.2(2)	C(8) -C(13)	-C(12) 122.5(2)
C(15)	-C(3)	-C(2)	109.2(2)	C(16) -C(15)	-C(20) 118.6(2)
C(5)	-C(4)	-C(21)	120.3(2)	C(16) -C(15)	-C(3) 121.6(2)
C(5)	-C(4)	-C(3)	126.7(2)	C(20) -C(15)	-C(3) 119.8(2)
C(21)	-C(4)	-C(3)	112.9(2)	C(15) -C(16)	-C(17) 120.4(2)
C(4)	-C(5)	-C(6)	128.2(2)	C(18) -C(17)	-C(16) 120.3(2)
C(5)	-C(6)	-C(7)	112.1(2)	C(19) -C(18)	-C(17) 119.3(2)
C(1)	-C(7)	-C(6)	113.9(2)	C(18) -C(19)	-C(20) 120.6(2)
C(13)	-C(8)	-C(9)	117.2(2)	C(19) -C(20)	-C(15) 120.7(2)

TABLE 5. Torsion angles (°) with standard uncertainties in parentheses.

O(1)	-C(1)	-C(2)	-C(8)	-33.7(3)	C(2)	-C(8)	-C(9)	-C(10)	179.0(2)
C(7)	-C(1)	-C(2)	-C(8)	147.4(2)	C(8)	-C(9)	-C(10)	-C(11)	-1.2(3)
O(1)	-C(1)	-C(2)	-C(3)	91.4(2)	C(14)	-O(2)	-C(11)	-C(12)	-8.8(3)
C(7)	-C(1)	-C(2)	-C(3)	-87.5(2)	C(14)	-O(2)	-C(11)	-C(10)	170.9(2)
C(8)	-C(2)	-C(3)	-C(4)	171.2(2)	C(9)	-C(10)	-C(11)	-O(2)	-179.3(2)
C(1)	-C(2)	-C(3)	-C(4)	44.6(2)	C(9)	-C(10)	-C(11)	-C(12)	0.4(3)
C(8)	-C(2)	-C(3)	-C(15)	-62.0(2)	O(2)	-C(11)	-C(12)	-C(13)	-179.8(2)
C(1)	-C(2)	-C(3)	-C(15)	171.5(2)	C(10)	-C(11)	-C(12)	-C(13)	0.5(3)
C(15)	-C(3)	-C(4)	-C(5)	-110.3(2)	C(9)	-C(8)	-C(13)	-C(12)	-0.3(3)
C(2)	-C(3)	-C(4)	-C(5)	15.9(3)	C(2)	-C(8)	-C(13)	-C(12)	-178.1(2)
C(15)	-C(3)	-C(4)	-C(21)	68.0(2)	C(11)	-C(12)	-C(13)	-C(8)	-0.5(3)
C(2)	-C(3)	-C(4)	-C(21)	-165.8(2)	C(4)	-C(3)	-C(15)	-C(16)	-124.5(2)
C(21)	-C(4)	-C(5)	-C(6)	178.3(2)	C(2)	-C(3)	-C(15)	-C(16)	105.0(2)
C(3)	-C(4)	-C(5)	-C(6)	-3.5(4)	C(4)	-C(3)	-C(15)	-C(20)	57.3(3)
C(4)	-C(5)	-C(6)	-C(7)	-60.2(3)	C(2)	-C(3)	-C(15)	-C(20)	-73.2(3)
O(1)	-C(1)	-C(7)	-C(6)	-150.3(2)	C(20)	-C(15)	-C(16)	-C(17)	1.7(3)
C(2)	-C(1)	-C(7)	-C(6)	28.6(3)	C(3)	-C(15)	-C(16)	-C(17)	-176.6(2)
C(5)	-C(6)	-C(7)	-C(1)	52.4(3)	C(15)	-C(16)	-C(17)	-C(18)	-0.1(4)

C(1) -C(2) -C(8) -C(13) -122.9(2) C(16) -C(17) -C(18) -C(19) -1.3(4)

C(3) -C(2) -C(8) -C(13) 113.2(2) C(17) -C(18) -C(19) -C(20) 1.1(4)

C(1) -C(2) -C(8) -C(9) 59.3(3) C(18) -C(19) -C(20) -C(15) 0.5(4)

C(3) -C(2) -C(8) -C(9) -64.5(2) C(16) -C(15) -C(20) -C(19) -1.9(4)

C(13) -C(8) -C(9) -C(10) 1.2(3) C(3) -C(15) -C(20) -C(19) 176.4(2)

TABLE 6. Anisotropic atomic displacement parameters ($Å^2$).

ATOM	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.028(1)	0.073(1)	0.051(1)	-0.0025(8)	0.0016(7)	0.0038(8)
O(2)	0.049(1)	0.075(1)	0.037(1)	-0.0044(8)	0.0010(8)	-0.0125(8)
C(1)	0.031(1)	0.048(1)	0.041(1)	0.006(1)	0.002(1)	0.003(1)
C(2)	0.024(1)	0.044(1)	0.044(1)	0.001(1)	0.004(1)	-0.002(1)
C(3)	0.027(1)	0.041(1)	0.045(1)	0.001(1)	-0.002(1)	-0.002(1)
C(4)	0.034(1)	0.047(2)	0.043(2)	0.002(1)	0.001(1)	0.005(1)
C(5)	0.039(1)	0.061(2)	0.042(2)	0.000(1)	-0.003(1)	0.007(1)
C(6)	0.039(1)	0.055(2)	0.048(2)	-0.009(1)	0.002(1)	-0.005(1)
C(7)	0.042(1)	0.048(2)	0.050(2)	-0.002(1)	0.004(1)	0.004(1)
C(8)	0.027(1)	0.041(1)	0.039(1)	0.002(1)	0.001(1)	0.002(1)
C(9)	0.027(1)	0.046(1)	0.042(2)	0.002(1)	0.003(1)	-0.004(1)
C(10)	0.027(1)	0.047(1)	0.046(2)	-0.002(1)	-0.002(1)	-0.003(1)
C(11)	0.036(1)	0.046(1)	0.039(2)	0.000(1)	-0.001(1)	0.002(1)
C(12)	0.036(1)	0.049(1)	0.043(2)	0.001(1)	0.007(1)	-0.004(1)
C(13)	0.031(1)	0.044(1)	0.048(2)	0.000(1)	0.001(1)	-0.006(1)
C(14)	0.047(2)	0.070(2)	0.039(2)	-0.001(1)	0.001(1)	0.004(1)
C(15)	0.028(1)	0.047(1)	0.041(1)	0.002(1)	-0.002(1)	0.002(1)

C(16) 0.043(2) 0.051(2) 0.042(2) -0.003(1) -0.003(1) 0.002(1)
C(17) 0.067(2) 0.055(2) 0.044(2) -0.002(1) 0.001(1) 0.014(1)
C(18) 0.046(2) 0.070(2) 0.055(2) 0.008(2) 0.010(1) 0.017(1)
C(19) 0.033(2) 0.070(2) 0.081(2) 0.000(2) 0.004(1) 0.002(1)
C(20) 0.032(2) 0.052(2) 0.072(2) -0.009(1) 0.005(1) -0.001(1)
C(21) 0.075(2) 0.063(2) 0.053(2) 0.005(1) 0.000(1) 0.013(1)

The anisotropic displacement parameter exponent takes the form:

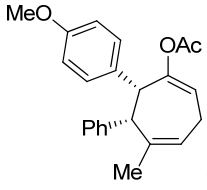
$-2\bullet^{2}(h^{2}a^{*2}U^{11}+k^{2}b^{*2}U^{22}+ \ldots +2hka^{*}b^{*}U^{12})$

TABLE 7. Hydrogen atom coordinates and displacement parameters.

ATOM	x	y	z	U_{iso}
H(2)	0.758	0.754	0.383	0.045
H(3)	0.879	0.922	0.354	0.045
H(5)	0.747	0.797	0.223	0.057
H(61)	0.755	0.657	0.253	0.057
H(62)	0.693	0.691	0.311	0.057
H(71)	0.917	0.621	0.327	0.056
H(72)	0.997	0.677	0.281	0.056
H(9)	1.063	0.894	0.424	0.046
H(10)	1.118	0.930	0.513	0.048
H(12)	0.765	0.791	0.565	0.051
H(13)	0.715	0.753	0.475	0.050
H(141)	0.795	0.900	0.634	0.078
H(142)	0.930	0.899	0.676	0.078
H(143)	0.880	0.810	0.647	0.078
H(16)	0.758	1.025	0.409	0.054
H(17)	0.548	1.081	0.451	0.066
H(18)	0.324	1.007	0.442	0.068
H(19)	0.311	0.881	0.389	0.074
H(20)	0.519	0.826	0.346	0.062
H(211)	0.761	0.943	0.219	0.096
H(212)	0.862	0.988	0.265	0.096
H(213)	0.687	0.988	0.271	0.096

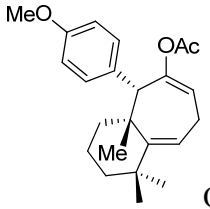
5. Characterization of 7-membered rings

(1*E*,4*Z*)-7-(4-Methoxyphenyl)-5-methyl-6-phenylcyclohepta-1,4-dienyl acetate (4aA)



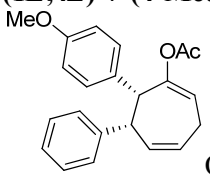
Obtained in 85% yield using conditions III. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.21 (m, 3H), 7.05-7.00 (m, 4H), 6.76 (dt, *J* = 2.0, 8.8 Hz, 2H), 5.71 (d, *J* = 7.6 Hz, 1H), 5.57 (dd, *J* = 2.8, 8.4 Hz, 1H), 4.09 (s, 1H), 4.03 (s, 1H), 3.80 (s, 3H), 3.34 (dd, *J* = 2.8, 19.6 Hz, 1H), 2.80 (dt, *J* = 8.0, 19.6 Hz, 1H), 1.77 (s, 3H), 1.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 158.6, 150.8, 141.3, 139.8, 131.6, 131.5, 130.4, 127.7, 126.6, 122.8, 115.9, 113.1, 55.1, 51.8, 50.5, 24.9, 24.8, 20.7 ppm; IR (neat, ν/cm^{-1}): 3028, 2961, 2835, 2359, 2335, 1749, 1682, 1608, 1510, 1447, 1302, 1254, 1223, 1181, 1087, 1035, 832, 806, 701, 535; HRMS (ESI): m/z: calcd for $C_{23}H_{24}NaO_3^+$: 371.1618, found: 371.1617.

(6*E*,9*Z*)-2,3,4,4a,5,8-Hexahydro-5-(4-methoxyphenyl)-1,1,4a-trimethyl-1H-benzo[7]annulen-6-yl acetate (4aB)



Obtained in 59% yield using conditions III. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (dt, *J* = 3.2, 8.8 Hz, 2H), 6.76 (dt, *J* = 3.2, 8.8 Hz, 2H), 5.65 (dd, *J* = 2.8, 7.2 Hz, 1H), 5.36 (d, *J* = 9.2 Hz, 1H), 3.77 (s, 3H), 3.19-3.11 (m, 1H), 3.10-3.00 (m, 2H), 1.99 (s, 3H), 1.83-1.74 (m, 1H), 1.65-1.54 (m, 1H), 1.45-1.35 (m, 4H), 1.32-1.25 (m, 1H), 1.18-1.12 (m,1H), 1.03 (s, 3H), 1.00-0.95 (m, 1H), 0.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 158.4, 150.3, 149.9, 133.5, 131.7, 119.8, 114.1, 112.7, 59.6, 55.1, 42.3, 36.9, 36.8, 35.4, 33.4, 30.5, 27.9, 27.8, 21.3, 16.9 ppm; IR (neat, ν/cm^{-1}): 2958, 2935, 2869, 1763, 1608, 1509, 1463, 1366, 1251, 1181, 1094, 1034, 830, 734; HRMS (ESI): m/z: calcd for $C_{23}H_{30}NaO_3^+$: 377.2087, found: 377.2084.

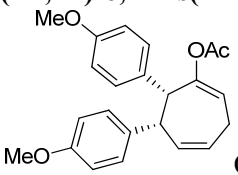
(1*E*,4*Z*)-7-(4-Methoxyphenyl)-6-phenylcyclohepta-1,4-dienyl acetate (4aC)



Obtained in 92% yield using conditions II. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21-7.17 (m, 3H), 6.90-6.87 (m, 2H), 6.75 (dt, *J* = 2.8, 9.2 Hz, 2H), 6.68 (dt, *J* = 2.8, 9.2 Hz, 2H), 6.01-5.96 (m, 1H), 5.87-5.81 (m, 1H), 5.61 (dd, *J* = 2.8, 8.0 Hz, 1H), 4.44 (s, 1H), 3.77 (s, 3H), 3.64 (t, *J* = 3.2 Hz, 1H), 3.33 (d, *J* = 20.0 Hz, 1H), 2.87 (dt, *J* = 8.0, 19.6 Hz, 1H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 158.6, 150.9, 142.2, 133.0, 131.4, 129.6,

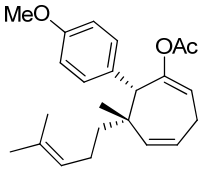
128.7, 128.5, 127.9, 126.4, 116.4, 112.6, 55.1, 53.5, 47.0, 25.0, 21.0 ppm; IR (neat, ν/cm^{-1}): 3031, 2930, 2834, 1748, 1682, 1607, 1509, 1455, 1368, 1246, 1214, 1176, 1101, 1034, 907, 820, 736, 700, 583, 519; HRMS (ESI): m/z: calcd for $C_{22}H_{22}NaO_3^+$: 357.1461, found: 357.1461.

(1*E*,4*Z*)-6,7-Bis(4-methoxyphenyl)cyclohepta-1,4-dienyl acetate (4aD)



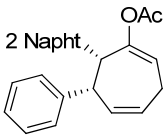
Obtained in 77% yield using conditions II. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80-6.68 (m, 8H), 5.99-5.93 (m, 1H), 5.80-5.75 (m, 1H), 5.76 (dd, *J* = 2.8, 7.6 Hz, 1H), 4.38 (s, 1H), 3.77 (s, 6H), 3.61 (t, *J* = 3.2 Hz, 1H), 3.31 (d, *J* = 20.0 Hz 1H), 2.85 (dt, *J* = 7.6, 20.0 Hz, 1H), 1.92 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 158.5, 158.1, 150.9, 134.4, 133.4, 131.4, 129.7, 129.6, 128.3, 116.3, 113.2, 112.5, 55.2, 55.1, 53.6, 46.1, 24.9, 20.9 ppm; IR (neat, ν/cm^{-1}): 3034, 2997, 2934, 2834, 1745, 1609, 1509, 1462, 1368, 1244, 1215, 1176, 1099, 1032, 907, 828, 792, 732, 527; HRMS (ESI): m/z: calcd for $C_{23}H_{24}NaO_4^+$: 387.1567, found: 387.1566.

(1*E*,4*Z*)-7-(4-Methoxyphenyl)-6-methyl-6-(4-methylpent-3-enyl)cyclohepta-1,4-dienyl acetate (4aE)



Obtained in 37% yield using conditions IV.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.74-5.69 (m, 1H), 5.45 (dd, *J* = 2.8, 11.6 Hz, 1H), 5.40-5.38 (m, 1H), 4.95 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.28 (s, 1H), 3.17-3.09 (m, 1H), 2.93 (t, *J* = 6.4, 22.4 Hz, 1H), 2.06-1.84 (m, 5H), 1.63 (s, 3H), 1.55 (s, 3H), 1.39 (s, 3H), 1.14-1.06 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 158.4, 150.3, 138.3, 132.6, 131.1, 131.0, 126.2, 124.6, 114.7, 113.0, 57.3, 55.1, 42.0, 40.5, 26.9, 25.7, 24.3, 22.5, 21.1, 17.6 ppm; IR (neat, ν/cm^{-1}): 2965, 2926, 2854, 1748, 1608, 1509, 1454, 1302, 1220, 1178, 1097, 1065, 1036, 816, 692; HRMS (ESI): m/z: calcd for $C_{23}H_{30}NaO_3^+$: 377.2087, found: 377.2089.

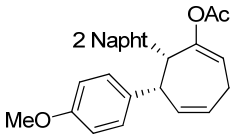
(1*E*,4*Z*)-7-(Naphthalen-3-yl)-6-phenylcyclohepta-1,4-dienyl acetate (4bC)



Obtained in 72% yield using conditions II. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80-7.78 (m, 1H), 7.66-7.61 (m, 2H), 7.46-7.40 (m, 2H), 7.23 (s, 1H), 7.19-7.13 (m, 3H), 7.02 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.87 (dd, *J* = 2.0, 8.0 Hz, 2H), 6.08-6.02 (m, 1H), 5.87-5.83 (m, 1H), 5.71 (dd, *J*

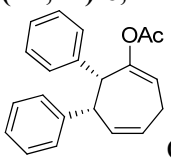
= 2.8, 8.0 Hz, 1H), 4.56 (s, 1H), 3.89 (t, *J* = 3.6 Hz, 1H), 3.40 (d, *J* = 20.0 Hz, 1H), 2.96 (dt, *J* = 8.0, 20.0 Hz, 1H), 1.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 150.5, 141.9, 135.1, 132.8, 132.7, 132.6, 129.4, 128.8, 128.7, 128.7, 128.0, 127.9, 127.5, 126.5, 126.5, 125.6, 125.5, 116.9, 54.5, 47.0, 24.9, 20.9 ppm; IR (neat, ν/cm^{-1}): 3057, 3030, 2926, 2360, 2342, 1731, 1598, 1453, 1369, 1214, 1041, 859, 819, 735, 700, 478; HRMS (ESI): m/z: calcd for $C_{25}H_{22}NaO_2^+$: 377.1512, found: 377.1511.

(1*E*,4*Z*)-6-(4-Methoxyphenyl)-7-(naphthalen-3-yl)cyclohepta-1,4-dienyl acetate (4bD)



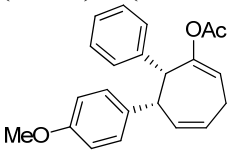
Obtained in 55% yield using conditions II.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80-7.78 (m, 1H), 7.68-7.66 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.45-7.40 (m, 2H), 7.26 (s, 1H), 7.02 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 6.77 (dt, *J* = 8.8 Hz, *J* = 2.4 Hz, 2H), 6.69 (dt, *J* = 8.8 Hz, *J* = 2.4 Hz, 2H), 6.05-5.99 (m, 1H), 5.81-5.77 (m, 1H), 5.70 (dd, *J* = 8.0 Hz, *J* = 2.8 Hz, 1H), 4.51 (s, 1H), 3.85 (t, *J* = 3.2 Hz, 1H), 3.76 (s, 3H), 3.37 (d, *J* = 19.6 Hz, 1H), 2.93 (dt, *J* = 20.0 Hz, *J* = 7.6 Hz, 1H), 1.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 158.2, 150.6, 135.3, 134.2, 133.3, 132.7, 132.6, 129.7, 129.4, 128.8, 128.5, 127.9, 127.5, 126.5, 125.6, 125.5, 116.9, 113.3, 55.2, 54.6, 46.2, 24.9, 21.0 ppm; IR (neat, ν/cm^{-1}): 3053, 2936, 2834, 1748, 1610, 1511, 1368, 1247, 1217, 1179, 1101, 1035, 909, 800, 748, 733, 478; HRMS (ESI): m/z: calcd for $C_{26}H_{24}NaO_3^+$: 407.1618, found: 407.1618.

(1*E*,4*Z*)-6,7-Diphenylcyclohepta-1,4-dienyl acetate (4cC)



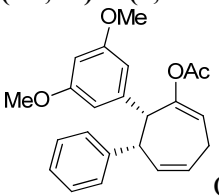
Obtained in 80% yield using conditions II. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.12 (m, 6H), 6.89-6.83 (m, 4H), 6.04-5.98 (m, 1H), 5.87-5.82 (m, 1H), 5.65 (dd, *J* = 3.2, 8.0 Hz, 1H), 4.49 (s, 1H), 3.72 (t, *J* = 3.2 Hz, 1H), 3.34 (d, *J* = 20.0 Hz, 1H), 2.89 (dt, *J* = 8.0, 20.0 Hz, 1H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 150.6, 142.0, 137.5, 132.8, 130.4, 128.7, 128.6, 127.9, 127.2, 126.9, 126.5, 116.6, 54.3, 46.8, 24.9, 20.9 ppm; IR (neat, ν/cm^{-1}): 3059, 3029, 2356, 2331, 1749, 1600, 1492, 1453, 1214, 1101, 1051, 907, 738, 698, 514; HRMS (ESI): m/z: calcd for $C_{21}H_{20}NaO_2^+$: 327.1356, found: 327.1358.

(1*E*,4*Z*)-6-(4-Methoxyphenyl)-7-phenylcyclohepta-1,4-dienyl acetate (4cD)



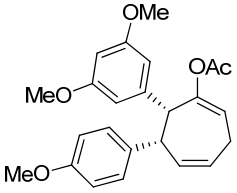
Obtained in 50% yield using conditions II. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16-7.12 (m, 1H), 7.11-7.06 (m, 2H), 6.80-6.77 (m, 2H), 6.74-6.70 (m, 2H), 6.68-6.65 (m, 2H), 5.95-5.89 (m, 1H), 5.75-5.70 (m, 1H), 5.57 (dd, *J* = 2.8, 7.6 Hz, 1H), 4.38-4.35 (m, 1H), 3.71 (s, 3H), 3.61 (t, *J* = 3.6 Hz, 1H), 3.27 (d, *J* = 19.6 Hz, 1H), 2.81 (dt, *J* = 7.6, 20.0 Hz, 1H), 1.86 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 158.2, 150.7, 137.7, 134.3, 133.3, 130.5, 129.6, 128.4, 127.2, 126.8, 116.6, 113.3, 55.2, 54.3, 46.0, 24.9, 21.0 ppm; IR (neat, ν/cm^{-1}): 3029, 2999, 2834, 2360, 2340, 1750, 1610, 1511, 1442, 1367, 1247, 1217, 1102, 1034, 827, 742, 702, 541; HRMS (ESI): m/z: calcd for $C_{22}H_{22}NaO_3^+$: 357.1461, found: 357.1461.

(1*E*,4*Z*)-7-(3,5-Dimethoxyphenyl)-6-phenylcyclohepta-1,4-dienyl acetate (4dC)



Obtained in 74% yield using conditions II. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.15 (m, 3H), 6.95-6.93 (m, 2H), 6.31 (t, *J* = 2.0 Hz, 1H), 6.01-5.86 (m, 3H), 5.90-5.86 (m, 1H), 5.63 (dd, *J* = 2.8, 7.6 Hz, 1H), 4.46 (s, 1H), 3.65 (t, *J* = 3.2 Hz, 1H), 3.61 (s, 6H), 3.32 (d, *J* = 19.2 Hz, 1H), 2.86 (dt, *J* = 7.6, 19.6 Hz, 1H), 1.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 159.5, 150.4, 142.1, 139.9, 132.8, 128.7, 128.5, 127.9, 126.5, 116.8, 108.6, 99.3, 55.1, 54.6, 46.7, 24.9, 21.0 ppm; IR (neat, ν/cm^{-1}): 3002, 2958, 2939, 2836, 2359, 2337, 1748, 1594, 1455, 1429, 1368, 1290, 1203, 1154, 1102, 1063, 840, 801, 752, 700; HRMS (ESI): m/z: calcd for $C_{23}H_{24}NaO_4^+$: 387.1567, found: 387.1569.

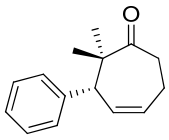
(1*E*,4*Z*)-7-(3,5-Dimethoxyphenyl)-6-(4-methoxyphenyl)cyclohepta-1,4-dienyl acetate (4dD)



Obtained in 44% yield (90% purity) using conditions II. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86-6.82 (m, 2H), 6.76-6.73 (m, 2H), 6.31 (t, *J* = 2.4 Hz, 1H), 6.01 (d, *J* = 2.4 Hz, 2H), 5.99-5.93 (m, 1H), 5.85-5.79 (m, 1H), 5.62 (dd, *J* = 3.2, 8.0 Hz, 1H), 4.40 (s, 1H), 3.76 (s, 3H), 3.64-3.60 (m, 7H), 3.35-3.26 (m, 1H), 2.86 (dt, *J* = 7.6, 20.0 Hz, 1H), 1.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 159.6, 158.24, 150.5, 140.1, 134.3, 133.3, 129.7, 128.3, 116.8, 113.3, 108.7, 99.2, 55.3, 55.2, 54.7, 45.9, 24.9, 21.1 ppm; IR (neat, ν/cm^{-1}): 2999, 2956,

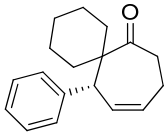
2936, 2835, 1748, 1594, 1512, 1460, 1428, 1368, 1291, 1247, 1204, 1155, 1102, 1058, 912, 826, 793, 714; HRMS (ESI): m/z: calcd for $C_{24}H_{26}NaO_5^+$: 417.1672, found: 417.1670.

(*Z*)-2,2-Dimethyl-3-phenylcyclohept-4-enone (5eC)



Obtained in 52% yield using conditions V. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.23 (m, 5H), 65.94-5.89 (m, 1H), 5.68-5.62 (m, 1H), 4.16-4.13 (m, 1H), 3.50-3.43 (m, 1H), 2.60-2.40 (m, 3H), 1.04 (s, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.1, 140.7, 133.9, 130.0, 128.7, 127.9, 126.7, 55.2, 50.2, 36.8, 27.6, 25.4, 18.6 ppm; IR (neat, ν/cm^{-1}): 3027, 2972, 2929, 2904, 1702, 1493, 1465, 1450, 1377, 1317, 1240, 1194, 1135, 1094, 1032, 894, 759, 727, 705, 646; HRMS (ESI): m/z: calcd for $C_{15}H_{18}NaO^+$: 237.1250, found: 237.1247.

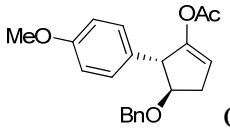
(*Z*)-(2,2-Spirocyclohexyl)-3-phenylcyclohept-4-enone (5fC)



Obtained in 79% yield using conditions V. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-7.22 (m, 3H), 7.16-7.14 (m, 2H), 5.93-5.91 (m, 2H), 3.28 (t, *J* = 2.8 Hz, 1H), 2.79-2.73 (m, 1H), 2.68-2.62 (m, 1H), s.53-2.45 (m, 1H), 2.32-2.24 (m, 1H), 2.19-2.10 (m, 2H), 1.62-1.47 (m, 4H), 1.29-1.20 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.0, 141.0, 134.5, 129.9, 129.2, 127.9, 126.7, 57.6, 53.8, 38.7, 34.3, 30.3, 26.1, 25.8, 23.5, 23.3 ppm; IR (neat, ν/cm^{-1}): 3025, 2929, 2852, 2360, 1691, 1492, 1448, 1191, 1082, 914, 751, 703, 640, 483; HRMS (EI): m/z: calcd for $C_{18}H_{22}NaO^+$: 254.1671, found: 254.1672.

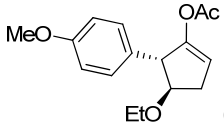
6. Characterization of 5-membered rings

4-(Benzyloxy)-5-(4-methoxyphenyl)cyclopent-1-enyl acetate (3aJ)



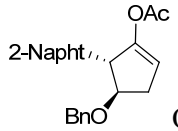
Obtained as a single diastereoisomer in 83% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.33-7.26 (m, 5H), 7.13-7.11 (m, 2H), 6.88-6.85 (m, 2H), 5.64-5.63 (m, 1H), 4.56 (dd, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.13-4.08 (m, 2H), 3.81 (s, 3H), 2.83-2.77 (m, 1H), 2.53-2.49 (m, 1H), 1.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 158.5, 149.2, 138.2, 132.4, 128.8, 128.3, 127.6, 127.5, 114.0, 111.6, 85.4, 71.0, 56.0, 55.2, 34.9, 20.9 ppm; IR (neat, ν/cm^{-1}): 3031, 2942, 2908, 2836, 1754, 1611, 1510, 1369, 1246, 1204, 1176, 1034, 906, 727; MS (ESI): m/z for $C_{21}H_{22}NaO_4^+$: 361.2.

4-Ethoxy-5-(4-methoxyphenyl)cyclopent-1-enyl acetate (3aK)



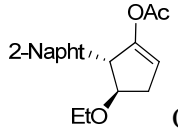
Obtained as a single diastereoisomer in 75% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.12-7.09 (m, 2H), 6.86-6.83 (m, 2H), 5.62 (dd, *J* = 2.3, 4.2 Hz, 1H), 4.01-3.99 (m, 1H), 3.98-3.94 (m, 1H), 3.79 (s, 3H), 3.55-3.36 (m, 2H), 2.82-2.75 (m, 1H), 2.44-2.38 (m, 1H), 1.94 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 158.4, 149.2, 132.6, 128.8, 113.9, 111.6, 85.7, 64.4, 55.9, 55.2, 35.0, 20.9, 15.4 ppm; IR (neat, ν/cm^{-1}): 2974, 2932, 2901, 2832, 1755, 1611, 1509, 1369, 1246, 1201, 1175, 1088, 1033, 827; HRMS (ESI): m/z calcd for $C_{16}H_{20}NaO_4^+$: 299.1254, found: 299.1253.

4-(Benzyloxy)-5-(naphthalene-2-yl)cyclopent-1-enyl acetate (3bJ)



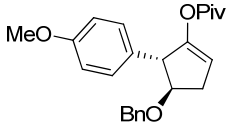
Obtained as a single diastereoisomer in 79% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.86-7.82 (m, 3H), 7.67 (s, 1H), 7.52-7.46 (m, 2H), 7.35-7.24 (m, 6H), 5.75-5.74 (m, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.37-4.36 (m, 1H), 4.23 (m, 1H), 2.92-2.86 (m, 1H), 2.61-2.57 (m, 1H), 1.92 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 148.9, 138.2, 137.9, 133.5, 132.5, 128.4, 128.3, 127.7, 127.6, 127.6, 127.5, 126.6, 126.1, 126.0, 125.6, 112.1, 85.3, 71.2, 57.1, 35.1, 20.9 ppm; IR (neat, ν/cm^{-1}): 3054, 3025, 2912, 2856, 1757, 1648, 1600, 1454, 1368, 1198, 1091, 1071, 1012, 817, 740, 698; HRMS (ESI): m/z calcd for $C_{24}H_{22}NaO_3^+$: 381.1461, found: 381.1461.

4-Ethoxy-5-(naphthalene-2-yl)cyclopent-1-enyl acetate (3bK)



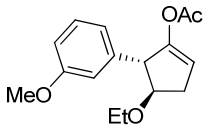
Obtained as a single diastereoisomer in 73% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.83-7.80 (m, 3H), 7.66 (d, *J* = 1.1 Hz, 1H), 7.46 (m, 2H), 7.33 (dd, *J* = 1.7, 8.5 Hz, 1H), 5.72 (dd, *J* = 2.3, 4.4 Hz, 1H), 4.24-4.23 (m, 1H), 4.09 (td, *J* = 3.9, 7.6 Hz, 1H), 3.58-3.37 (m, 2H), 2.88 (tdd, *J* = 2.2, 7.2, 16.4 Hz, 1H), 2.49 (dddd, *J* = 1.6, 2.4, 4.0, 16.5 Hz, 1H), 1.90 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 148.9, 138.1, 133.5, 132.5, 128.4, 127.7, 127.6, 126.6, 126.1, 125.9, 125.6, 112.1, 85.6, 64.6, 57.0, 35.3, 20.9, 15.4 ppm; IR (neat, ν/cm^{-1}): 3050, 2975, 2870, 1759, 1648, 1600, 1508, 1369, 1201, 1092, 906, 818, 730; HRMS (ESI): m/z calcd for $C_{19}H_{20}NaO_3^+$: 319.1305, found: 319.1304.

4-(Benzyloxy)-5-(4-methoxyphenyl)cyclopent-1-enyl pivalate (3gJ)



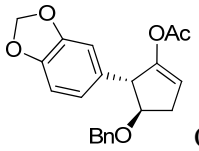
Obtained as a single diastereoisomer in 82% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.33-7.24 (m, 5H), 7.14-7.10 (m, 2H), 6.87-6.83 (m, 2H), 6.56-6.55 (m, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.20-4.17 (m, 2H), 3.81 (s, 3H), 2.83-2.76 (m, 1H), 2.55-2.47 (m, 1H), 0.99 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.7, 158.5, 149.4, 138.3, 132.6, 129.1, 128.2, 127.5, 127.4, 113.8, 111.0, 85.8, 71.1, 55.7, 55.2, 38.8, 34.8, 26.7 ppm; IR (neat, ν/cm^{-1}): 3031, 2972, 2933, 2907, 2871, 1747, 1611, 1510, 1455, 1248, 1177, 1109, 908, 827, 698; HRMS (ESI): m/z calcd for $C_{24}H_{28}NaO_4^+$: 403.1882, found: 403.1879.

4-Ethoxy-5-(3-methoxyphenyl)cyclopent-1-enyl acetate (3hK)



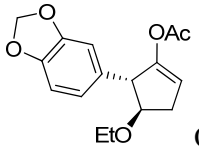
Obtained as a single diastereoisomer in 60% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.23 (t, *J* = 7.9 Hz, 1H), 6.80-6.74 (m, 3H), 5.65 (dd, *J* = 2.2, 4.2 Hz, 1H), 4.02-3.96 (m, 2H), 3.80 (s, 3H), 3.58-3.38 (m, 2H), 2.80 (tdd, *J* = 2.3, 7.1, 16.4 Hz, 1H), 2.46-2.40 (m, 1H), 1.96 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 159.8, 148.8, 142.3, 129.6, 120.2, 113.5, 112.1, 112.0, 85.4, 64.4, 56.9, 55.2, 35.2, 20.9, 15.4 ppm; IR (neat, ν/cm^{-1}): 2974, 2942, 2896, 2837, 1757, 1599, 1584, 1486, 1369, 1264, 1202, 1091, 1045, 783, 700; HRMS (ESI): m/z calcd for $C_{16}H_{20}NaO_4^+$: 299.1257, found: 299.12534.

5-(Benzo[d][1,3]dioxol-5-yl)-4-(benzyloxy)cyclopent-1-enyl acetate (3iJ)



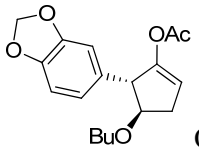
Obtained as a single diastereoisomer in 87% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.34-7.27 (m, 5H), 6.78-6.76 (m, 1H), 6.69-6.67 (m, 2H), 5.95 (s, 2H), 5,65-5.64 (m, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.10-4.06 (m, 2H), 2.79 (tdd, *J* = 2.0, 6.8, 16.3 Hz, 1H), 2.53-2.48 (m, 1H), 1.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.1, 148.9, 147.8, 146.4, 138.2, 134.2, 128.3, 127.5, 127.4, 121.0, 111.8, 108.3, 107.9, 100.9, 85.3, 71.0, 56.5, 34.8, 20.9 ppm; IR (neat, ν/cm^{-1}): 3029, 2902, 1755, 1503, 1486, 1441, 1368, 1199, 1094, 1071, 1037, 932, 807, 737, 698; HRMS (ESI): m/z calcd for $C_{21}H_{20}NaO_5^+$: 375.1201, found: 375.1203.

5-(Benzo[*d*][1,3]dioxol-5-yl)-4-ethoxycyclopent-1-enyl acetate (3iK)



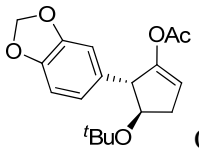
Obtained as a single diastereoisomer in 87% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 6.74 (d, *J* = 7.7 Hz, 1H), 6.67-6.64 (m, 2H), 5.94-5.93 (m, 2H), 5.62 (dd, *J* = 2.2, 4.2 Hz, 1H). 3.97-3.96 (m, 1H), 3.93 (td, *J* = 3.8, 7.5 Hz, 1H), 3.54-3.38 (m, 2H), 2.77 (tdd, *J* =2.3, 7.1, 16.4 Hz, 1H), 2.42-2.38 (m, 1H), 1.97 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 149.0, 147.8, 146.4, 134.5, 121.0, 111.8, 108.3, 107.9, 100.9, 85.6, 64.4, 56.5, 35.0, 20.9, 15.4 ppm; IR (neat, ν/cm^{-1}): 2974, 2886, 1756, 1504, 1486, 1441, 1369, 1202, 1098, 1038, 931, 807, 729; HRMS (ESI): m/z calcd for $C_{16}H_{18}NaO_5^+$: 313.1048, found: 313.1046.

5-(Benzo[d][1,3]dioxol-5-yl)-4-butoxycyclopent-1-enyl acetate (3iL)



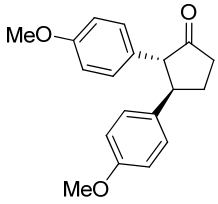
Obtained as a single diastereoisomer in 59% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 6.74 (d, *J* = 7.7 Hz, 1H), 6.66-6.64 (m, 2H), 5.93 (s, 2H), 5.61 (m, 1H), 3.96-3.95 (m, 1H), 3.91 (td, *J* = 3.8, 7.4 Hz, 1H), 3.39 (tdd, *J* = 6.6, 9.1, 35.3 Hz, 2H), 2.76 (tdd, *J* = 2.1, 7.1, 16.4 Hz, 1H), 2.41-2.37 (m, 1H), 1.97 (s, 3H), 1.45-1.48 (m, 2H), 1.39-1.30 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 149.0, 147.8, 146.3, 134.5, 121.0, 111.9, 108.3, 107.9, 100.9, 85.8, 68.9, 56.5, 34.9, 31.9, 20.9, 19.3, 13.8 ppm; IR (neat, ν/cm^{-1}): 2957, 2931, 2872, 1757, 1504, 1486, 1441, 1368, 1246, 1200, 1095, 1038, 1012, 934, 807, 578; HRMS (ESI): m/z calcd for $C_{18}H_{22}NaO_5^+$: 341.1359, found: 341.1359.

5-(Benzo[d][1,3]dioxol-5-yl)-4-*tert*-butoxycyclopent-1-enyl acetate (3iM)



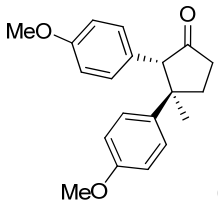
Obtained as a single diastereoisomer in 87% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 6.73 (d, *J* = 7.8 Hz, 1H), 6.65-6.61 (m, 2H), 5.93 (dd, *J* = 1.4, 2.9 Hz, 2H), 5.57 (dd, *J* = 2.4, 4.5 Hz, 1H), 4.00 (td, *J* = 4.8, 7.4 Hz, 1H), 3.86-3.84 (m, 1H), 2.76-2.69 (m, 1H), 2.35 (tdd, *J* = 2.1, 4.5, 16.1 Hz, 1H), 1.95 (s, 3H), 1.04 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.1, 148.6, 147.7, 146.2, 134.4, 121.2, 111.9, 108.1, 108.0, 100.8, 79.1, 73.6, 58.1, 37.9, 28.4, 20.9 ppm; IR (neat, ν/cm^{-1}): 2972, 2933, 2900, 1757, 1659, 1504, 1486, 1440, 1364, 1249, 1204, 1186, 1080, 1038, 931, 872, 806, 727, 633, 575; HRMS (ESI): m/z calcd for $C_{18}H_{22}NaO_5^+$: 341.1359, found: 341.1359.

2,3-Bis(4-methoxyphenyl)cyclopentanone (6aF)



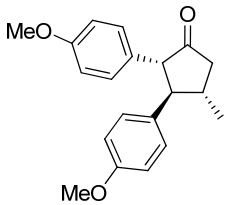
Obtained as a single diastereoisomer in 90% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.11-7.08 (m, 2H), 6.97-6.94 (m, 2H), 6.83-6.79 (m, 4H), 3.77 (s, 3H), 3.75 (s, 3H), 3.45-3.33 (m, 2H), 2.71-2.63 (m, 1H), 2.51-2.40 (m, 2H), 2.17-2.00 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 217.1, 158.5, 158.4, 133.7, 129.6, 129.1, 128.0, 114.0, 113.9, 62.3, 55.2, 55.1, 49.7, 38.6, 29.5 ppm; IR (neat, ν/cm^{-1}): 2999, 2951, 2932, 2837, 1733, 1670, 1598, 1509, 1461, 1248, 1168, 1030, 825; HRMS (ESI): m/z calcd for $C_{19}H_{20}NaO_3^+$: 319.1305, found: 319.1305.

2,3-Bis(4-methoxyphenyl)-3-methylcyclopentanone (6aG)



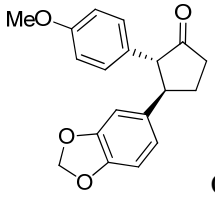
Obtained as a 7:1 mixture of diastereoisomers in 82% yield. (Major isomer): ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.22-7.18 (m, 2H), 6.87-6.83 (m, 2H), 6.80-6.73 (m, 4H), 3.81 (s, 3H), 3.76 (s, 3H), 3.66 (s, 1H), 2.66-2.50 (m, 3H), 2.15-2.09 (m, 1H), 1.18 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 217.4, 158.6, 157.9, 138.5, 131.4, 127.1, 126.7, 113.5, 113.4, 67.6, 55.2, 55.1, 47.3, 35.9, 34.6, 21.4 ppm; IR (neat, ν/cm^{-1}): 3037, 2957, 2835, 1734, 1610, 1511, 1462, 1245, 1180, 1132, 1031, 827, 733, 581; HRMS (ESI): m/z calcd for $C_{20}H_{22}NaO_3^+$: 333.1461, found: 333.1461.

2,3-Bis(4-methoxyphenyl)-4-methylcyclopentanone (6aH)



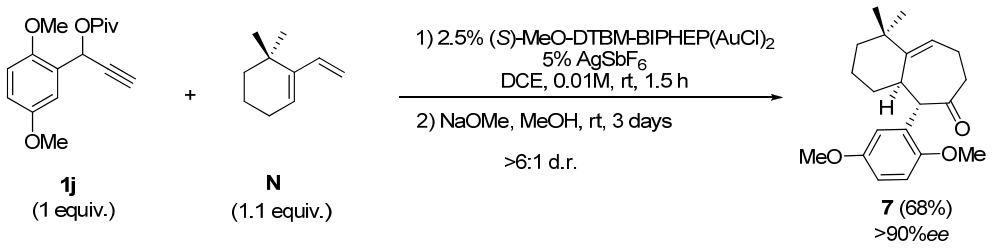
Obtained as a single diastereoisomer in 78% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.09-7.06 (m,2H), 6.92-6.89 (m, 2H), 6.84-6.75 (m, 4H), 3.77 (s, 3H), 3.73 (s, 3H), 3.46 (d, *J* = 12.5 Hz, 1H), 2.89-2.78 (m, 2H), 2.44-2.32 (m, 1H), 2.16-2.04 (m, 1H), 1.09 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 216.3, 158.5, 158.4, 132.1, 129.5, 129.2, 128.5, 113.9, 113.9, 63.8, 58.3, 55.2, 55.1, 47.0, 36.8, 17.9 ppm; IR (neat, ν/cm^{-1}): 3002, 2955, 2920, 2869, 2835, 1740, 1612, 1513, 1246, 1178, 1031, 881, 827; HRMS (ESI): m/z calcd for $C_{20}H_{22}NaO_3^+$: 333.1464, found: 333.1461.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)cyclopentanone (6aI)



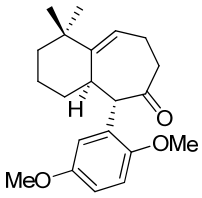
Obtained as a single diastereoisomer in 63% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ = 6.96 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.71-6.69 (m, 2H), 6.63-6.61 (m, 1H), 5.91 (s, 2H), 3.75 (s, 3H), 3.42-3.30 (m, 2H), 2.70-2.62 (m, 1H), 2.49-2.39 (m, 2H), 2.09-1.97 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 216.6, 158.6, 147.8, 146.3, 135.6, 129.6, 128.9, 120.2, 114.1, 108.3, 107.2, 100.9, 62.2, 55.1, 50.2, 38.5, 29.6 ppm; IR (neat, ν/cm^{-1}): 2957, 2934, 2897, 1737, 1611, 1512, 1505, 1441, 1403, 1243, 1179, 1115, 1034, 863, 824, 727, 549; HRMS (ESI): m/z calcd for $C_{19}H_{18}NaO_4^+$: 333.1097, found: 333.1095.

7. Characterization of Frondosin derivatives including ligand optimization



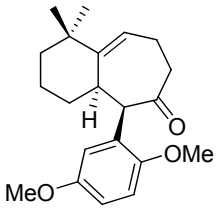
To a solution of the 1-(2,5-dimethoxyphenyl)prop-2-ynyl pivalate (**1j**) (0.05 mmol, 1.0 equiv.) and 6,6-dimethyl-1-vinylcyclohex-1-ene (**N**) (0.055 mmol, 1.1 equiv.) in 1,2-DCE (0.01 M), (*S*)-MeO-DBTM-BIPHEP(AuSbF$_6$)$_2$ (0.025 equiv.) was added. The mixture was stirred at room temperature for 90 minutes. The reaction was quenched with triethylamine (0.05 equiv.) and the solvent was removed under reduce pressure. Then NaOMe (3.0 equiv.) and methanol were added and the mixture was stirred at room temperature for 3 days. The reaction was quenched with a saturated solution of NH_4Cl and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduce pressure. The residue was purified by column chromatography (Hex: AcOEt 10:1) to give the corresponding ketone **7** (11.1 mg) in 68% yield (major isomer).

(4a*S*,5*R*,*E*)-5-(2,5-Dimethoxyphenyl)-1,1-dimethyl-1,2,3,4,4a,5,7,8-octahydrobenzo[7] annulen-6-one (Major Isomer-7)



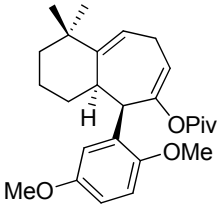
(Major isomer, 68% yield): ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.06 (d, *J* = 2.5 Hz, 1H), 6.78-6.73 (m, 2H), 5.64 (dd, *J* = 5.0, 8.8 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.95-2.86 (m, 1H), 2.80 (t, *J* = 11.3 Hz, 1H), 2.71-2.54 (m, 2H), 2.23-2.15 (m, 1H), 1.78-1.74 (m, 1H), 1.66-1.48 (m, 4H), 1.28-1.22 (m, 1H), 1.08 (s, 3H), 1.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.0, 153.6, 151.7, 150.4, 128.5, 117.4, 115.5, 111.3, 111.0, 56.1, 55.7, 49.6, 45.3, 42.4, 42.4, 38.5, 34.1, 30.4, 26.0, 22.7, 21.0 ppm; IR (neat, ν/cm^{-1}): 2927, 2861, 2834, 2369, 1709, 1589, 1493, 1462, 1278, 1216, 1049, 913, 806, 714; HRMS (ESI): m/z calcd for $C_{21}H_{28}NaO_3^+$: 351.1932, found: 351.1931; $[\alpha]^{25}_D$ -55.1 (c 0.37, $CHCl_3$).

(4a*R*,5*R*,*E*)-5-(2,5-Dimethoxyphenyl)-1,1-dimethyl-1,2,3,4,4a,5,7,8-octahydrobenzo[7] annulen-6-one (Minor Isomer-7)



(Minor isomer, 12% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 2.8 Hz, 1H), 6.81-6.74 (m, 2H), 5.65 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.17 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 2.93-2.83 (m, 2H), 2.67 (dt, *J* = 3.6, 18.8 Hz, 1H), 2.57-2.48 (m, 1H), 2.30-2.21 (m, 1H), 2.10-2.04 (m, 1H), 1.67-1.59 (m, 2H), 1.55-1.49 (m, 1H), 1.30-1.22 (m, 1H), 1.11 (s, 3H), 1.09 (s, 3H), 1.04-0.96 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.2, 153.3, 151.3, 151.3, 129.3, 117.6, 116.3, 111.1, 111.0, 56.1, 55.7, 48.1, 44.0, 42.9, 40.3, 38.8, 32.2, 30.3, 26.1, 23.1, 22.9 ppm; IR (neat, ν/cm^{-1}): 2927, 2861, 2834, 2369, 2338, 1709, 1589, 1493, 1462, 1428, 1355, 1278, 1216, 1179, 1049, 1026, 913, 838, 714; HRMS (ESI): m/z: calcd for $C_{21}H_{28}NaO_3^+$: 351.1932, found: 351.1931.

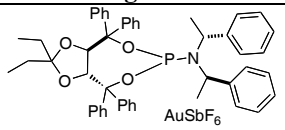
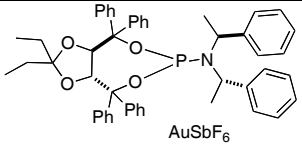
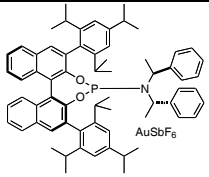
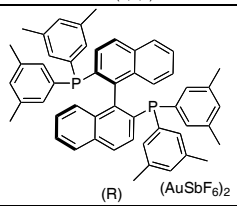
(4a*R*,5*R*,6*E*,9*E*)-5-(2,5-Dimethoxyphenyl)-1,1-dimethyl-2,3,4,4a,5,8-hexahydro-1*H*-benzo[7]annulen-6-yl pivalate

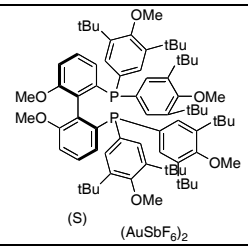


^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 2.8 Hz, 1H), 6.71-6.67 (m, 2H), 5.70-5.67 (m, 1H), 5.52 (dd, *J* = 3.6, 8.0 Hz, 1H), 4.34 (t, *J* = 2.8 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.23-3.19 (m, 1H), 3.13-3.05 (m, 1H), 2.70 (dt, *J* = 8.0, 18.8 Hz, 1H), 1.88-1.80 (m, 1H), 1.70-1.61 (m, 1H), 1.50-1.35 (m, 2H), 1.27-1.21 (m, 1H), 1.03 (s, 3H), 0.99-0.93 (m, 10H), 0.76 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 152.9, 152.5, 151.3, 149.8, 130.1, 119.1, 117.5, 114.9, 111.5, 110.5, 55.8, 55.7, 42.8, 39.4, 39.0, 38.8, 36.4, 31.1, 30.4, 29.1, 26.8, 24.4, 20.5 ppm; IR (neat, ν/cm^{-1}): 2955, 2934, 2866, 2832, 1740, 1495, 1462, 1417, 1364, 1278, 1216, 1177, 1126, 1050, 1028, 903, 803, 706; HRMS (ESI): m/z: calcd for $C_{26}H_{36}NaO_4^+$: 435.2506, found: 435.2501.

Table 4. Optimization of Chiral Ligands for reaction shown in Eq. 3.

The reaction conditions are those shown in Eq. 3: **1j** (1 equiv.), **N** (1.1 equiv.), [Au] (5 mol%), 1,2-DCE, r.t., 1.5 h (concentration 0.1 M), followed by in situ hydrolysis/equilibration to ketone **7** upon treatment with excess of NaOMe/MeOH at 25ºC for 48 h.

Ligand	ee (%)
 (R,R,R)	19
 (R,S,S)	7
 (S,S,S)	33
 (R)	33

	65 (>90)[a]

[a] Reaction concentration: 0.01 M

8. References

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Chapter 5

Gold-Catalyzed Cycloisomerization of 1-Cyclopropyl-alkynes

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Gold-Catalyzed Cycloisomerization of 1-Cyclopropyl-alkynes

D. Garayalde and C. Nevado*

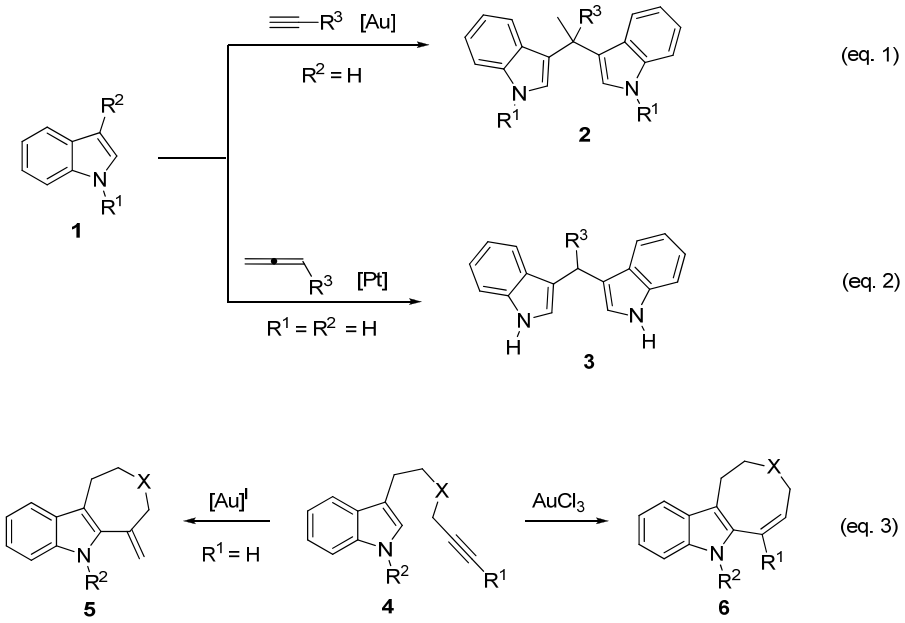
(Unpublished results)

5.1 Introduction

Transition metal-catalyzed hydroarylation of C-C multiple bonds has attracted considerable attention as an efficient approach to the functionalization of arenes. This interest has led to the development of a number of effective protocols for the hydroarylation of alkenes[1] and alkynes.[2] In this context, gold can act as a Lewis acid for the activation of alkynes towards a variety of nucleophiles under homogeneous catalysis conditions.[3] Reetz[4] and He[5] found independently that gold complexes are active catalysts for the intermolecular hydroarylation of electron-deficient alkynes.

Indoles and bis(indolyl)alkanes are important entities present in a large variety of natural products,[6] and have thus been already targeted in the context of gold catalysis. For example, Echavarren[7] and He[8] have developed methods where simple indoles **1** react intermoleculary with terminal alkynes in the presence of cationic gold(I) and gold(III) complexes respectively affording bisindolyl derivatives **2** (Scheme 1, eq. 1). Sierra and co-workers have expanded this chemistry using platinum catalysts with allenes as reaction counterparts (Scheme 1, eq. 2).[9] The mechanism of the addition of two molecules of indole to the terminal carbon atom of the allene seems to proceed *via* Pt-carbene intermediates in a similar manner than the previously reported platinum-catalyzed dihydroalkoxylation of monosubstituted allenes.[10]

Scheme 1. Gold- and silver-catalyzed synthesis of indolyl derivates

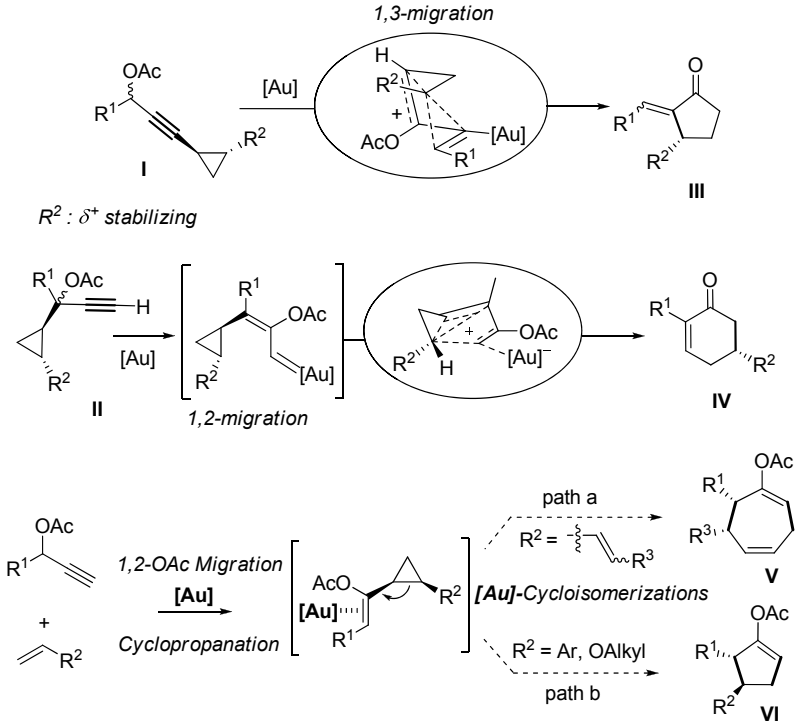


An intramolecular version of the reaction summarized in Scheme 1, eq. 1 has also been studied.[7] C2-substituted indoles react with alkynes in the presence of gold catalysts to give 7- and 8-membered rings (Scheme 1, eq. 3). The reaction outcome changes dramatically whether the

catalyst is gold(I) or gold(III). Substrates **4** cyclize readily with cationic gold(I) complexes to give azepino[4,5-*b*]indole derivates **5**[11] whereas the use of $AuCl_3$ leads to indoloazocines **6**.

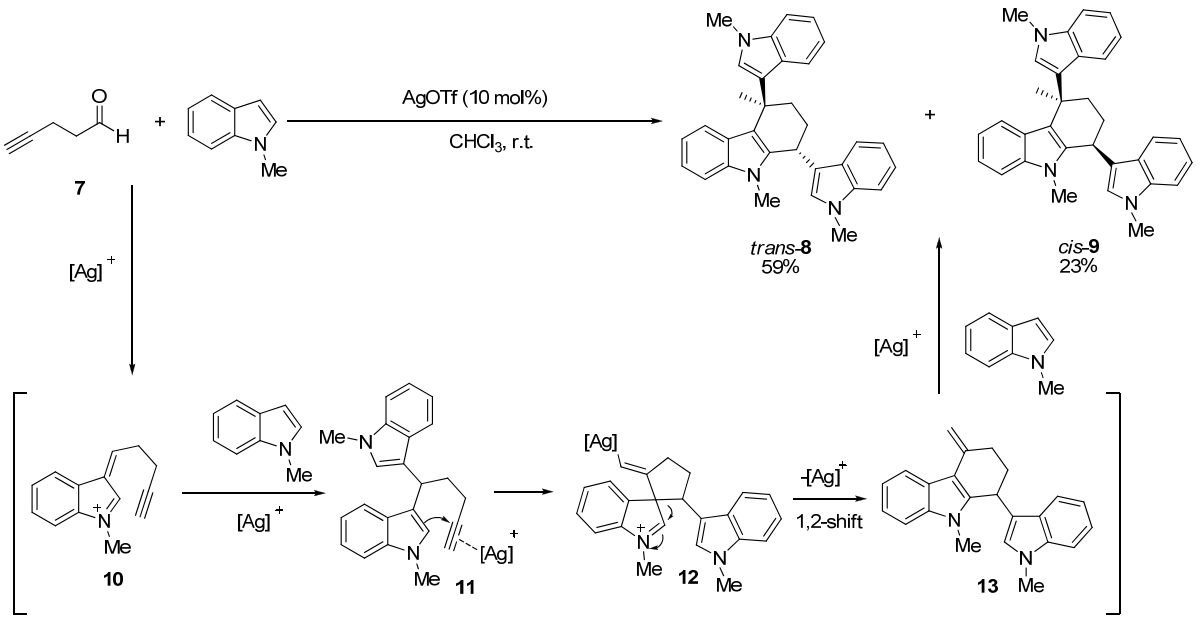
In the context of nucleophilic additions onto gold-activated alkynes, a well developed research area is the activation of propargyl carboxylates towards 1,2-acyloxy migration and/or [3,3]-sigmatropic rearrangement. This different reactivity is highly dependent on the substitution pattern of the alkyne.[12] In the last years, our research group has studied 3- and 1-substituted cyclopropyl propargyl acetates **I** and **II**, which in the presence of catalytic amounts of gold provided access to 5- and 6-membered ring respectively (**III** and **IV**).[13] Furthermore, two highly diastereoselective gold-catalyzed three-step cascade process for the synthesis of highly substituted 5- and 7-membered rings (**V** and **VI**) from propargyl acetates and alkenes or 1,4-dienes, have been also developed (Scheme 2).[14]

Scheme 2. Gold-catalyzed synthesis o f 5-, 6-, and 7-membered rings



Tetrahydrocarbazoles are common motifs found in many natural products and bioactive molecules.[15] Recently, a highly efficient method for the synthesis of substituted tetrahydrocarbazoles from pent-4-ynal and indoles using silver(I) catalysts has been reported (Scheme 3).[16] The mechanism associated to this transformation seems to involve the coordination of the silver salt onto the oxygen atom of the carbonyl group in **7** triggering the intermolecular nucleophilic attack of the indole and dehydration to give intermediate **10**. The attack of a second molecule of indole forms intermediate **11**, which cyclizes to give the spirocyclic iminium ion **12**. Intermediate **12**, undergoes a 1,2-carbon shift process to give the carbazole **13** in which the silver salt promotes the hydroarylation with a third molecule of indole to afford the final products **8** (*trans*) and **9** (*cis*) in a 59% and 23% yield respectively.

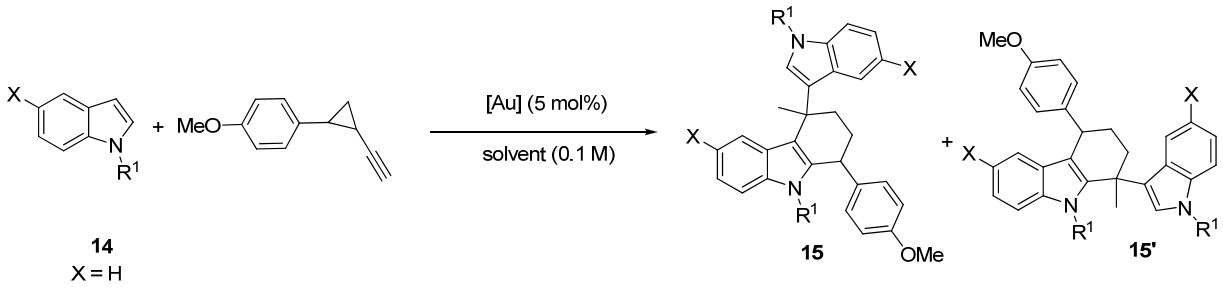
Scheme 3. Silver-catalyzed tandem reaction of acetylenic aldehydes **7** with indoles



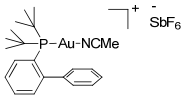
5.2 Results and discussion

With this background in hand, we decided to investigate more in depth the formation of highly substituted carbocycles using heteroaromatic nucleophiles such as indoles and stabilized cyclopropyl alkynes. Our study commenced with the optimization of the model reaction of 1-(2-ethynylcyclopropyl)-4-methoxybenzene with different *N*-protected indoles **14** in the presence of various gold catalysts. The results are summarized in Table 1.

Table 1. Screening of catalysts



Entry	R^1	Conditions	Product 15/15' Yield(%) / (d.r.)
1	(**14a**) Bn	$IPrAuNTf_2$, DCM, r.t, 48 h	No reaction
2	(**14a**) Bn	$Ph_3PAuNTf_2$, DCM, r.t. 48 h	Traces (**15/15')a**
3	(**14a**) Bn	$(t\text{-Bu})_3PAuNTf_2$, DCM, r.t 48 h	Traces (**15/15')a**

4	(**14a**) Bn	$(PhO)_3PAuSbF_6$, DCM, r.t. 3 h	Traces (**15/15'**)**a**
5	(**14a**) Bn	$(PhO)_3PAuSbF_6$, DCM, 50 °C, 72 h	Traces (**15/15'**)**a**
6	(**14a**) Bn	 **16** Toluene, r.t. 24 h	95% yield / (2:1) 6:1 regioisomeric ratio **15a:15'a**
7	(**14b**) Me	**16**,Toluene, r.t. 24 h	60 % yield / (2:1) 2:1 regioisomeric ratio **15b:15'b**
8	(**14b**) Me	**16**,Toluene, 80 °C, 12 h	88 % yield / (2:1) 4:1 regioisomeric ratio **15b:15'b**
9	(**14c**) H	**16**, Toluene, r.t. 24 h	No reaction
10	(**14c**) H	**16**, DCM, r.t. 24 h	No reaction
11	(**14c**) H	**16**, 1,2-DCE, 80 °C, 24 h	No reaction
12	(**14c**) H	**16**,THF, 100 °C, 12 h	92 % yield (1:1) 1:1 regioisomeric ratio **15c:15'c**

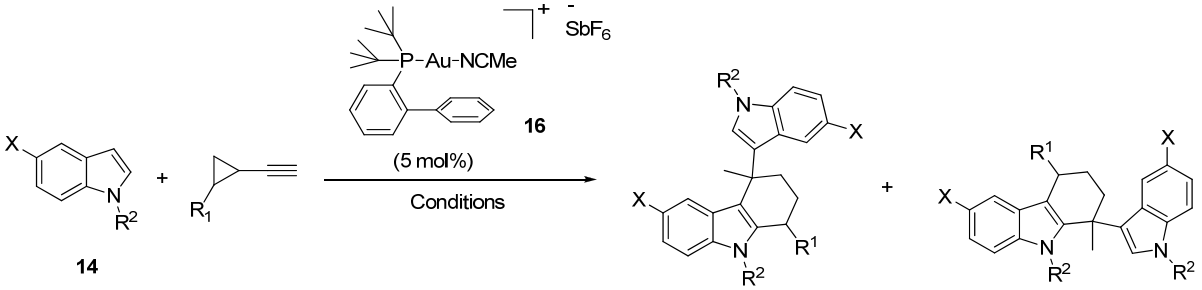
The reaction of 1-(2-ethynylcyclopropyl)-4-methoxybenzene with *N*-benzyl protected indole afforded no conversion or only traces of the desired products **15a** and **15'a** using gold catalysts either bearing σ-donating groups such as IPr (IPr = 1,3-bis(diisopropylphenyl)imidazol-2- ylidene) (entry 1), or better π-acceptors such as phosphine- and phosphite-based ligands (entry 2-5). We were pleased to find that using cationic gold complex **16** in toluene, a complete conversion of the starting materials into tetrahydrocarbazoles **15a** and **15'a** was observed (entry 6). The reaction was highly regioselective (6:1) favoring the 1-*p*-MeO-phenyl substituted tetrahydrocarbazole **15a**. Both **15a** and **15'a** where isolated as an unseparable 2:1 mixture of diastereoisomers. The same conditions were used for methyl-protected indole **14b** affording a 2:1 ratio of regioisomers **15b** and **15'b** isolated in 60% yield (entry 7). Upon heating the reaction to 80 °C a 4:1 regioisomeric mixture of the corresponding tetrahydrocarbazoles was obtained in 88% yield (entry 8).

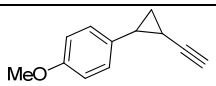
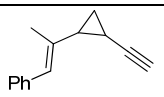
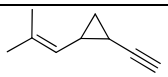
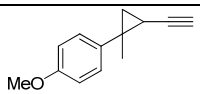
Having stablished cationic gold complex **16** as catalyst, we decided also to test these reaction conditions for non-protected indoles. Using the cationic gold complex **16** in toluene, dichloromethane and 1,2-dichloroethane as solvents, the reaction of parent indole showed no conversion to the products **15c** and **15'c** after prolongued stirring/heating (entries 9-11). Heating up the reaction to 100 °C in dry THF afforded a 1:1 mixture of regioisomers **15c** and **15'c** isolated in overall 92% yield (entry 12).

With the best conditions in hand, using catalyst **16** in toluene at 80 °C for *N*-protected indoles and catalyst **16** in THF at 100 °C for the non-protected ones, we then set out to explore the scope of this transformation. We focused on different *N*-protected indoles **14** in the presence of 1-

ethynylcyclopropyl derivates bearing substituents that are able to stabilize the positive electron density developed during the cyclopropyl-ring-opening process. The results are summarized in Table 2.

Table 2. Scope of the reaction with *N*-protected indoles



Entry	X	R^2	Alkyne	Product	Yield[a]	(d.r.) / (r.r)[d]	Yield[b,c]	(d.r.) / (r.r.)[d]
1	H	Bn (**14a**)		(**15a**)	95%	(2:1) / (6:1)	83%[b]	(2:1) / (12:1)
2	H	Me (**14b**)	"	(**15b**)	88%	(2:1) / (4:1)	74%[c]	(2:1) / (6:1)
3	H	*p*-$MeOC_6H_5$ (**14d**)	"	(**15d**)	76%	(2:1) / (7:1)	63%[b]	(2:1) / (7:1)
4	H	Cynnamyl (**14e**)	"	(**15e**)	78%	(2:1) / (10:1)	----	----
5	H	C_5H_{11} (**14f**)	"	(**15f**)	79%	(2:1) / (6:1)	75%[c]	(2:1) / (6:1)
6	OMe	Me (**14g**)	"	(**15g**)	86%	(2:1) / (2:1)	54%[c]	(2:1) / (2:1)
7	OMe	Bn (**14h**)	"	(**15h**)	56%	(2:1) / (3:1)	60%[b]	(2:1) /(3:1)
8	Br	Me (**14i**)	"	(**15i**)	72%	(2:1) / (8:1)	73%[c]	(2:1) / (8:1)
9	Br	Bn (**14j**)	"	(**15j**)	68%	(2:1) / (5:1)	76%[b]	(2:1) / (7:1)
10	Me	Me (**14k**)	"	(**15k**)	84%	(2:1) / (5:1)	77%[c]	(2:1) / (7:1)
11	Me	Bn (**14l**)	"	(**15l**)	42%	(2:1) / (3.5:1)	45%[b]	(2:1) / (5:1)
12	CN	Me (**14m**)	"	(**15m**)	52%	(2:1) / (2:1)	45%[c]	(2:1) / (5:1)
13	H	Bn (**14n**)		(**15n**)	81%	(1:1) / (5:1)	70%[b]	(1:1) / (5:1)
14	CN	Me (**14o**)	"	(**15o**)	79%	(5:1) / (7:1)	34%[c]	(5:1) / (7:1)
15	Br	Me (**14p**)	"	(**15p**)	82%	(1:1) / (5:1)	80 %	(1:1) / (12:1)
16	H	Bn (**14q**)		(**15q**)	57%	(1:1) / (5:1)	----	----
17	Br	Me (**14r**)	"	(**15r**)	69%	(1:1) / (5:1)	----	----
18	H	Bn (**14s**)		(**15s**)	63%	(1:1) / (5:1)	70%[b]	(1:1) / (8:1)
19	H	Me (**14t**)	"	(**15t**)	63%	(1:1) / (5:1)	56%[c]	(1:1) / (6:1)

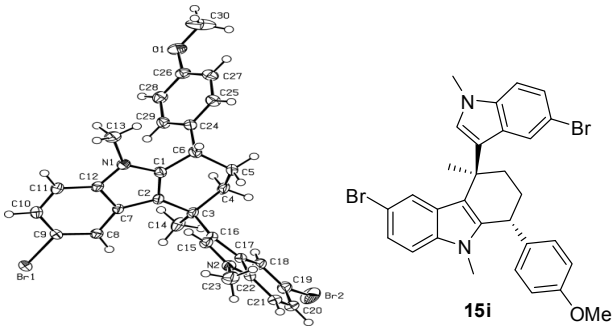
[a] Reaction conditions: Toluene (0.1M), 5 mol% catalyst **16,** 80 °C for 12h.
[b] Reaction conditions: Toluene (0.1M), 5 mol% catalyst **16**, 1.0 equiv. $NaHCO_3$, 80 °C for 12h.
[c] Reaction conditions: Toluene (0.1 M), 5 mol% catalyst **16**, 0.5 equiv. $NaHCO_3$, 80 °C for 12h.
[d] regioisomeric ratio.

The reaction tolerates different protecting groups at the nitrogen atom as well as different substituents at the 5-position of the indole counterpart. First, we tested the reaction of 1-(2-ethynylcyclopropyl)-4-methoxybenzene with different indoles, which yielded the corresponding tetrahydrocarbazoles **15a-m/15'a-m** in good yields (42-86% yield, entries 1-12) as 2:1 mixture of diastereoisomers with regioselectivities up to 12:1.

The scope of the reaction was expanded to study the effect of different stabilizing groups in the cyclopropyl alkyne upon reaction with benzyl- or methyl-protected indoles **14a** and **14b** respectively. When (*E*)-1-(2-(2-ethynylcyclopropyl)prop-1-enyl)benzene was tested, the reaction afforded the tetrahydrocarbazole derivates **15n-p/15'n-p** in yields up to 79% (entries 13-15). 1-Ethynyl-2-(2-methylprop-1-enyl)cyclopropane was also tested affording the corresponding products **15q-r/16'q-r** in yields up to 69% (entries 16-17). An additional methyl group at the cyclopropyl ring in the starting material was also tested affording, in the standard reaction conditions, the desired products **15s-t/15's-t** in 63% yield (entries 18-19). In these cases, the tetrahydrocarbazoles where obtained as a 1:1 mixture of diastereoisomers except for **15o/15'o** which gave a 5:1 diastereomeric mixture under the standard reaction conditions.

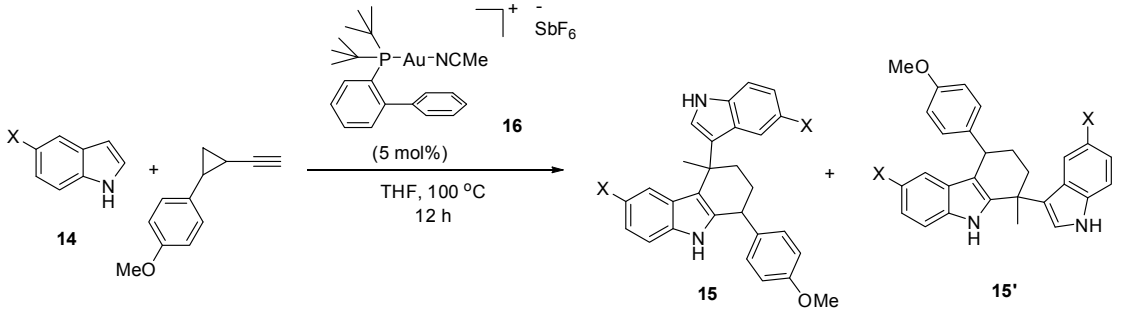
We then decided to run the reaction in presence of base in order to check if there could be an influence in the selectivity of the process. Remarkably, in all cases, the ratio between the regioisomers **15** and **15'** improve by the addition of 0.5 or 1.0 equivalents of $NaHCO_3$ depending on the substitution pattern on the indole. However, no improvement in the diastereoselectivity of the reaction was observed. The structure of the major regioisomer **15** was confirmed by bidimensional NMR experiments and X-ray diffraction analysis on compound **15i** (Figure 1).

Figure 1. X-Ray structure of tetrahydrocarbazole **15i** (Table 2, entry 8)



The scope of the reaction was expanded using indoles **14** without protecting group at the nitrogen atom. The results are summarized in Table 3.

Table 3. Scope of the reaction for non-protected indoles

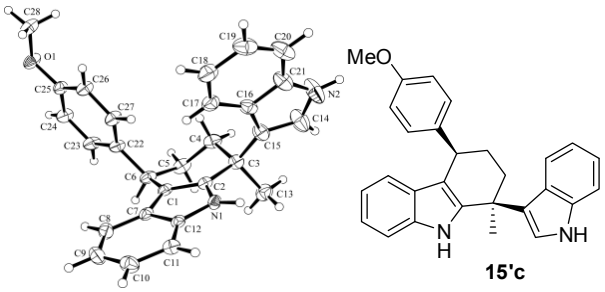


Entry	X	Product	Yield 15/15'[a,b]
1	H	**14c**	92%
2	Br	**14u**	71%
3	Me	**14v**	86%
4	CN	**14w**	68%

[a] 1:1 diastereomeric ratio, [b] 1:1 regioisomeric ratio.

Again, different substituents at the 5-position of the indole were tolerated for the reaction and the structure of the minor regioisomer **15'd** was confirmed by X-ray diffraction analysis (Figure 2). In sharp contrast with the reaction of *N*-protected indoles, the reaction of the non-protected indoles **14** showed to be no regioselective affording in all the cases a 1:1 mixture of the corresponding tetrahydrocarbazoles **15c,u-w** and their regioisomers **15'c,u-w**.

Figure 2. X-Ray structure of tetrahydrocarbazole **15'c** (Table 3, entry 1)

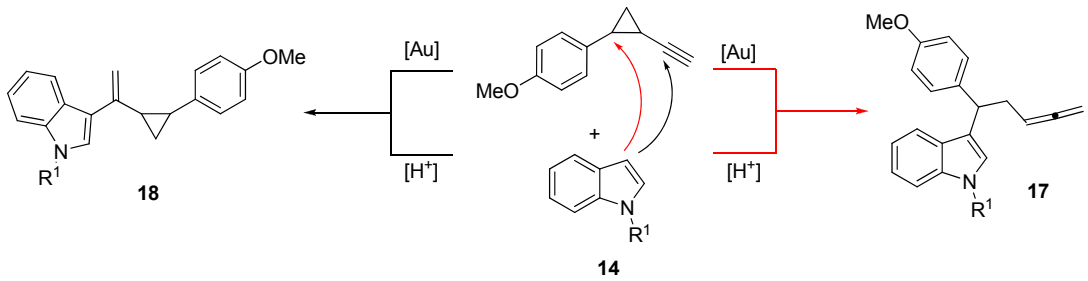


5.3 Mechanistic study

Based on the previously summarized experimental results, we decided to carry out a mechanistic study that takes into account the possibility of both gold- acid-catalyzed three step cascade reaction for the formation of tetrahydrocarbazoles **15** and **15'**. we considered that the reaction media becomes acidic upon the incorporation of the first indole molecule and as shown in Table 2 the use of base seems to influence the regioselectivity of the process.

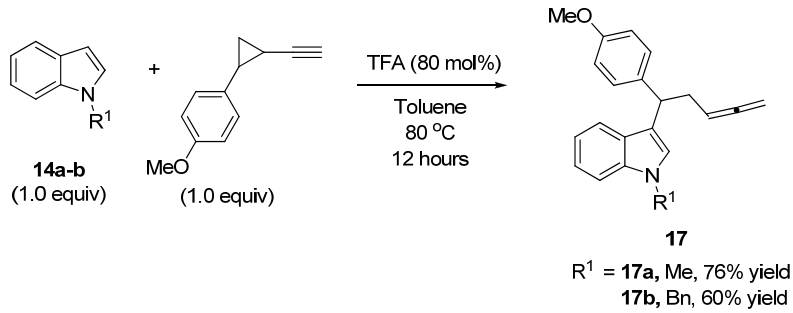
These transformations might commence with the nucleophilic attack of the indole **14** onto the gold- or acid-activated 1-(2-ethynylcyclopropyl)-4-methoxybenzene. Two distinct mechanistic scenarios arise from the different regioselectivity of the nucleophilic attack of the indole counterpart. Intermediate **18** can be formed by attack onto the internal position of the alkyne (Scheme 4, black arrow) whereas allene intermediate **17** would arise by attack of the indole onto the position 2 of the cyclopropyl ring (Scheme 4, red arrow).

Scheme 4. Divergent synthesis of **17** and **18**



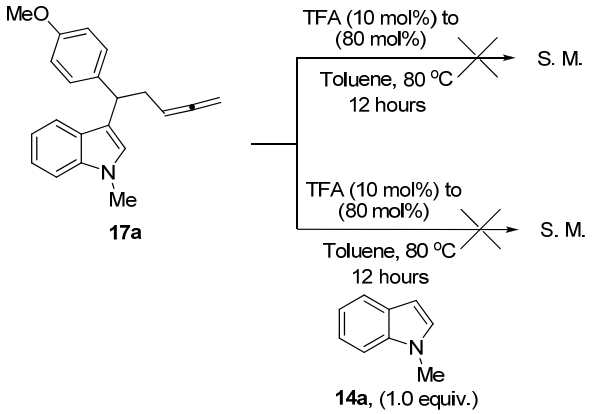
We thus decided to run the reaction between 1-(2-ethynylcyclopropyl)-4-methoxybenzene and methyl- or benzyl-indole **14a-b** in the presence of different amounts of protic acids (Scheme 5).[17] Using catalytic amounts of trifluoroacetic acid (10 mol%) allene **17** was detected although no total conversion could be achieved in spite of prolongued heating. However, the reaction with substoichiometric amounts of acid (80 mol%) was stirred in toluene for 12 hours at 80°C affording the allene intermediates **17** in good yields with total conversion of the starting materials.

Scheme 5. Synthesis of allene **17a-b**



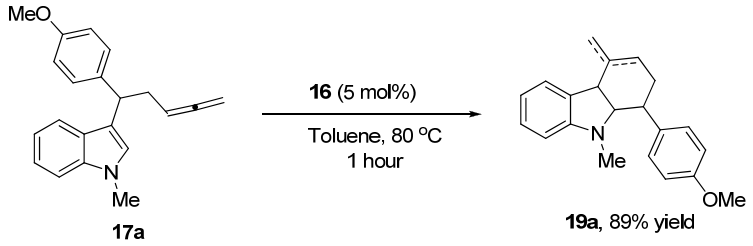
These reactions in presence of catalytic and substoichiometric amounts of acid do not evolve to the tetrahydrocarbazoles products confirming that these transformations cannot be a fully acid-catalyzed process. To confirm this hypothesis we decided to isolate allene intermediate **17a** and submit it to acidic conditions. The reaction of allene **17a** in presence of catalytic (10 mol%) and substoichiometric (80 mol%) amounts of TFA afforded no conversion even in the presence of 1 equivalent of methyl indole after heating the mixture at 80 °C for 12 hours (Scheme 6).

Scheme 6. Reaction of allene intermediate **17a** with acid



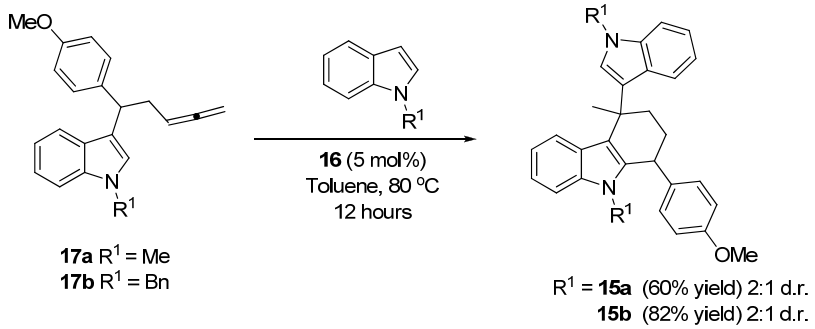
We then decided to run the reaction of allene intermediate **17a** in the presence of 5 mol% of the gold catalyst **16** (Scheme 7) heating in toluene at 80 °C. Total conversion into intermediate **19a** as a 2:1 regioisomeric mixture of *exo* and *endo* olefin was observed after one hour of reaction.

Scheme 7. Gold-catalyzed formation of **19a**



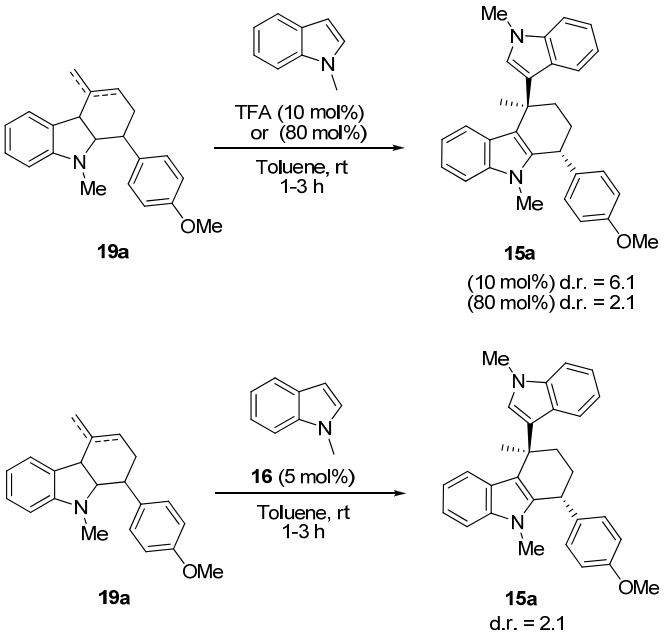
The fact that the formation of carbazole **19a** cannot be achieved by protic acid, confirms our hypothesis for the need of the gold catalyst in these transformations. Interestingly, the reaction of the allenyl intermediates **17a** and **17b** in presence of one equivalent of the corresponding indole and the gold catalyst **16** afforded, after 12 hours of reaction at 80°C, tetrahydrocarbazoles **15a-b** as single regioisomer in 60% to 82% yield as a 2:1 mixture of diastereoisomers (Scheme 8). Regioisomer **15** is the major one obtained in the reactions showed in Table 2.

Scheme 8. Gold-catalyzed reaction of allenes **17a-b** to form tetrahydrocarbazole **15a-b**



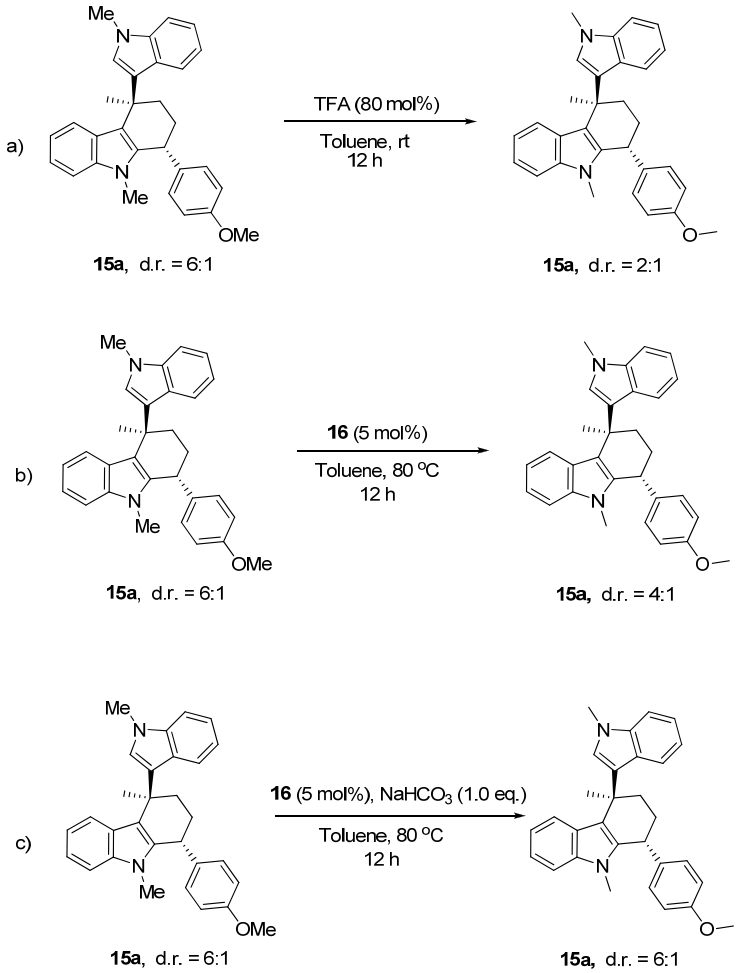
Interestingly, intermediate **19a**, obtained as a single regioisomer with a 2:1 *exo*:*endo* ratio of the olefin, reacted in presence of 10 mol% and 80 mol% of TFA and one equivalent of methyl indole to give the corresponding tetrahydrocarbazole **15a** as single regioisomer and 6:1 and 2:1 diastereomeric ratio respectively (Scheme 9). However, the reaction in presence of catalytic amounts of the gold catalyst afforded the tetrahydrocarbazole **15a** in 79% yield with a 2:1 diastereomeric ratio.

Scheme 9. Gold- and acid-catalyzed synthesis of tetrahydrocarbazole **15a**.



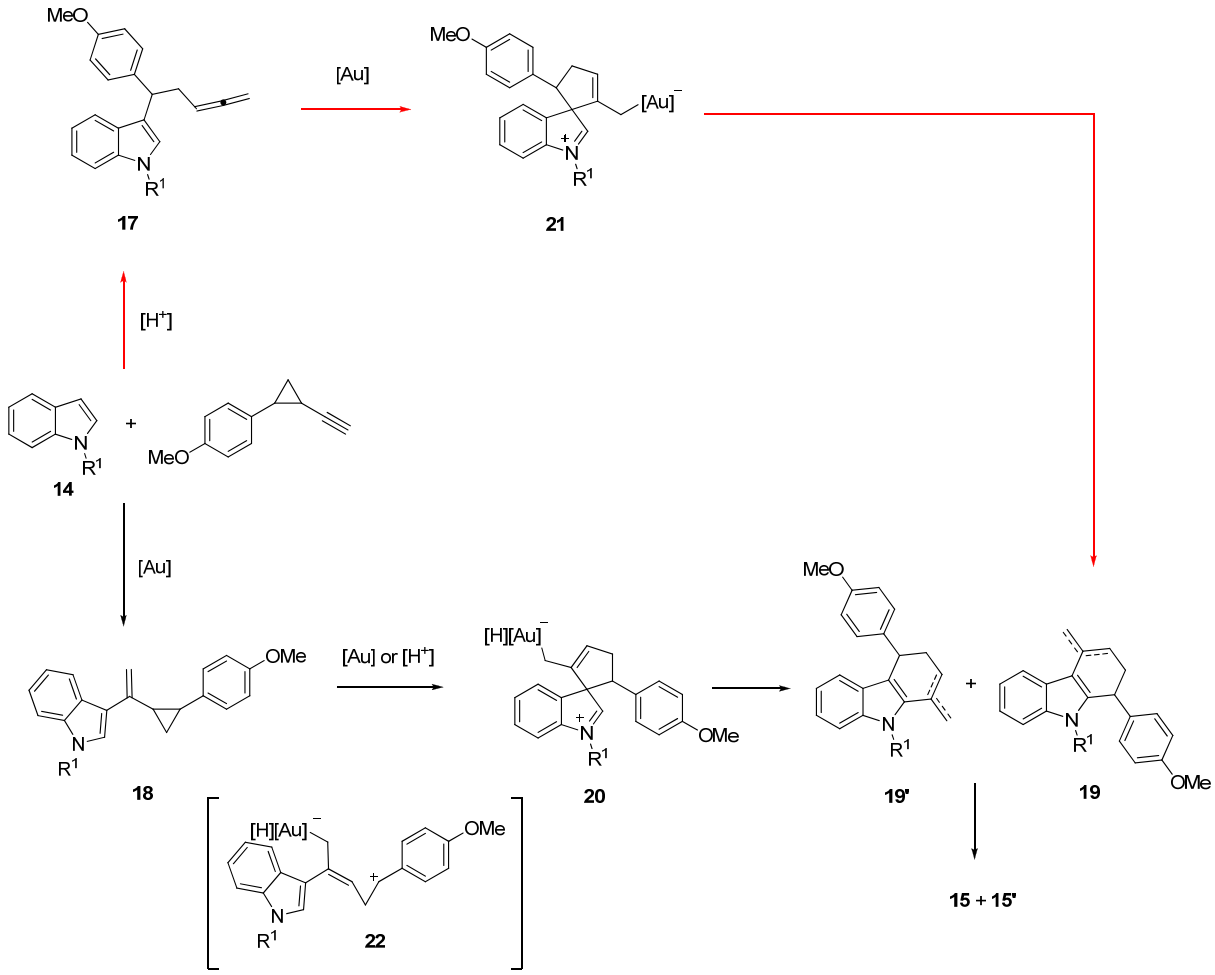
The non concordance with previous results, where the final products were obtained as a 2:1 diastereomeric mixture (Table 2), prompted us to think about the possibility of acid- or gold-catalyzed epimerization reaction at the benzylic position in the products. To corroborate this hypothesis, a 6:1 diastereomeric mixture of the tetrahydrocarbazole **15a**, obtained from the reaction of intermediate **19a** with 10 mol% of TFA, was treated with 80 mol% of acid (Scheme 10, a). After 12 hours at room temperature, epimerization at the benzylic position of the tetrahydrocarbazole **15a** was observed affording a 2:1 diastereomeric mixture. On the other hand, gold was also able to epimerize the benzylic position in **15a** (Scheme 10 b) from a diastereomeric ratio of 6:1 to 4:1. However, when 1 equivalent of $NaHCO_3$ was used in the later case (Scheme 10 c) no epimerization was observed confirming the need of acid to achieve this isomerization.

Scheme 10. Acid- and gold-catalyzed synthesis of tetrahydrocarbazole **15a**. Epimerization experiments



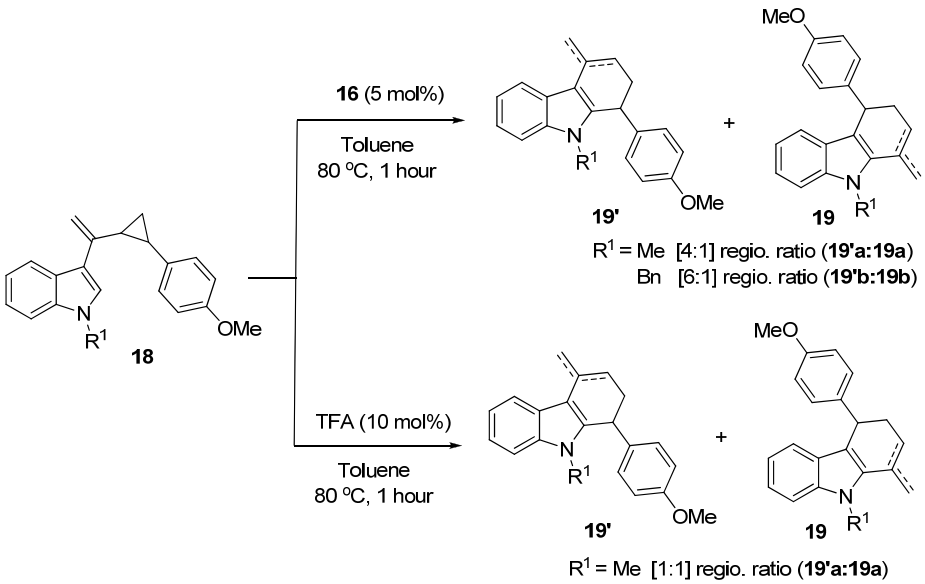
The experiment shown in Scheme 6 suggests that protic acid alone cannot explain the synthesis of tetrahydrocarbazoles **15** (showed in Table 1-3). However, as it was shown in Scheme 8, allene **17** might be involved in the formation of tetrahydrocarbazole **15** *via* **19** whose formation can only be achieved using gold catalysts (Scheme 7). In addition, the experiments with allene **17** in presence of acid and gold catalyst **16** cannot explain the formation of the minor regioisomer **15'** observed in Table 1-3. Thus, the alternative to explain the formation of the corresponding minor regioisomer **15'** is to look at intermediate **18**. As it was shown in Scheme 4, the possibility of a regioselective attack of the indole to the alkyne is an important issue.The formation of intermediates **19** and **19'** could be also explained from intermediate **18** (Scheme 11). As it was demonstrated in Schemes 5-8, allenyl intermediate **17** can only be transformed into carbazole intermediate **19** and tetrahydrocarbazoles **15** by gold catalysis (Scheme 11, red arrow). On the other hand, intermediate **18** can be activated in presence of both gold and acid triggering the cyclopropyl-ring opening and cyclizing intramoleculary to afford the spyrocyclic intermediate **20**. The lack of regioselectivity in the isomerization of this compound could explain a mixture of regioisomers **19** and **19'** (Scheme 11, black arrow) as intermediates for the synthesis of tetrahydrocarbazoles **15** and **15'**.

Scheme 11. Gold- and/or acid-catalyzed formation of carbazoles **19** and **19'**



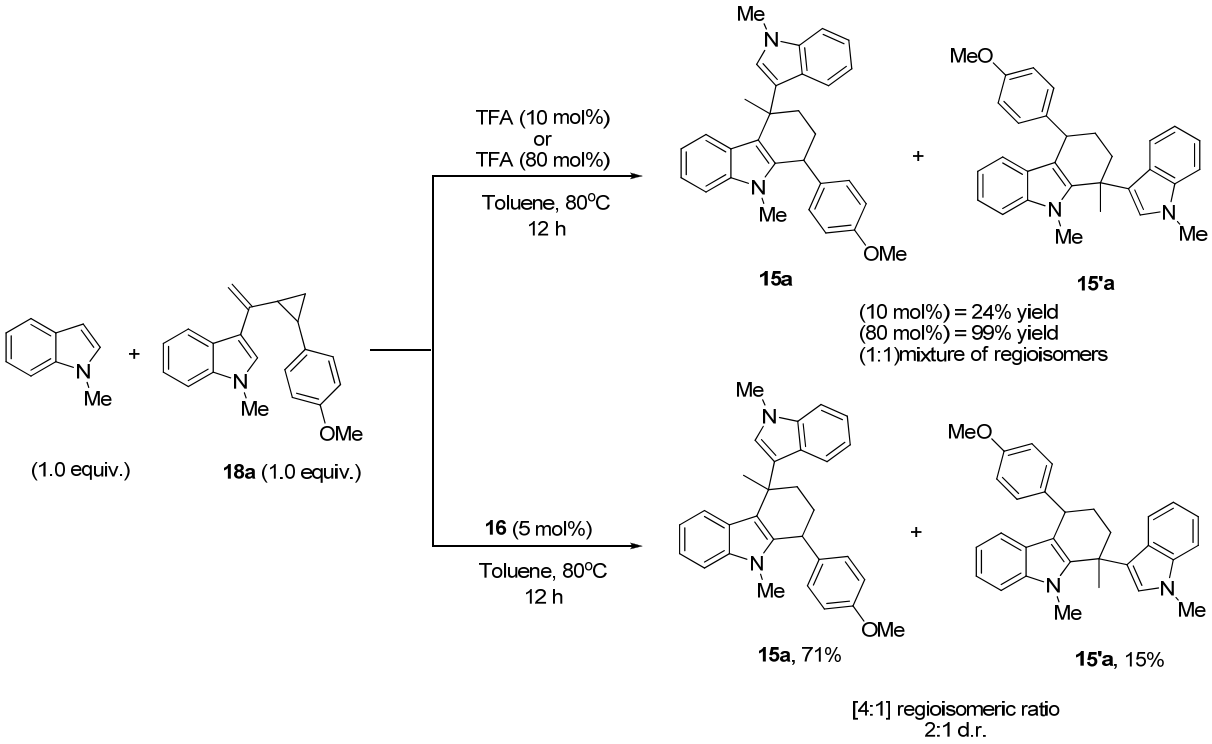
In order to study how intermediates **19** and **19'** are generated from **18**, we decided to run the following experiments. Intermediate **18** was synthetized and submitted independently to gold and acid catalysis (Schemes 12 and 13). The reaction of intermediate **18** in presence of catalytic amounts of the gold catalyst afforded different regioisomeric mixtures of intermediates **19** and **19'** after 1 hour of reaction at 80 ^{o}C (Scheme 12). *N*-Methyl protected intermediate **18a** afforded a 4:1 regioisomeric mixture of carbazole **19a** and **19'a** whereas *N*-benzyl protected intermediate **18b** afforded a 6:1 regioisomeric mixture of **19b** and **19'b**. On the other hand, the reaction of intermediate **18** in the presence of catalytic amounts of TFA afforded a 1:1 regioisomeric mixture of carbazoles **19a** and **19'a** after heating the reaction at 80 ^{o}C for 1 hour.

Scheme 12. Gold-catalyzed synthesis of **19** and **19'**



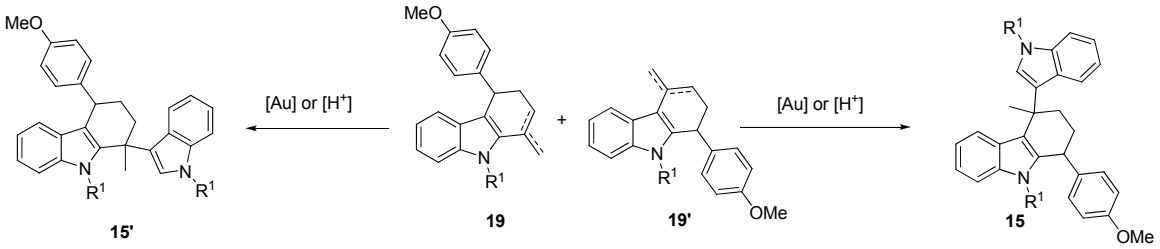
The possibility of a competitive acid-catalyzed mechanism for the formation of intermediates **19** and **19'** was confirmed through the following experiments. Intermediate **18a** was submitted under catalytic (10 mol%) and substoichiometric amounts of TFA (80 mol%) affording in both cases, after heating the reaction to 80 °C for 12 hours, a 1:1 regioisomeric mixture of tetrahydrocarbazoles **15a** and **15'a** (Scheme 13). The conversion of the reaction in presence of 10 mol% of TFA was not complete affording the mixture of products in 24% yield. However, the reaction in presence of substoichiometric amounts of TFA afforded total conversion after 12 hours of reaction and the mixture of products were obtained quantitatively. The formation of tetrahydrocarbazoles **15a** and **15'a** showed in Scheme 15 can be explained through the formation of carbazoles **19'** and **19** respectively. Further acid activation of the double bond in **19** and **19'** triggers the nucleophilic attack of a second molecule of indole affording the final products **15a** and **15'a**. Interestingly, the reaction of intermediate **18a** in the presence of 5 mol% of the gold catalyst **16** afforded a 4:1 regioisomeric mixture of tetrahydrocarbazoles **15a** and **15'a** isolated in 71% and 15% yield respectively.

Scheme 13. Acid-catalyzed synthesis of tetrahydrocarbazoles **15a** and **15'a**



For the last step of our mechanism, we hypothesize that the formation of tetrahydrocarbazoles **15** and **15'** can be catalyzed by the presence of acid and/or gold catalysts *via* regioisomeric mixture of carbazoles **19** and **19'** (Scheme 14). Gold and/or acid activate the unsaturated moiety in **19** or **19'** triggering a nucleophilic attack of a second molecule of indole to form the corresponding products.

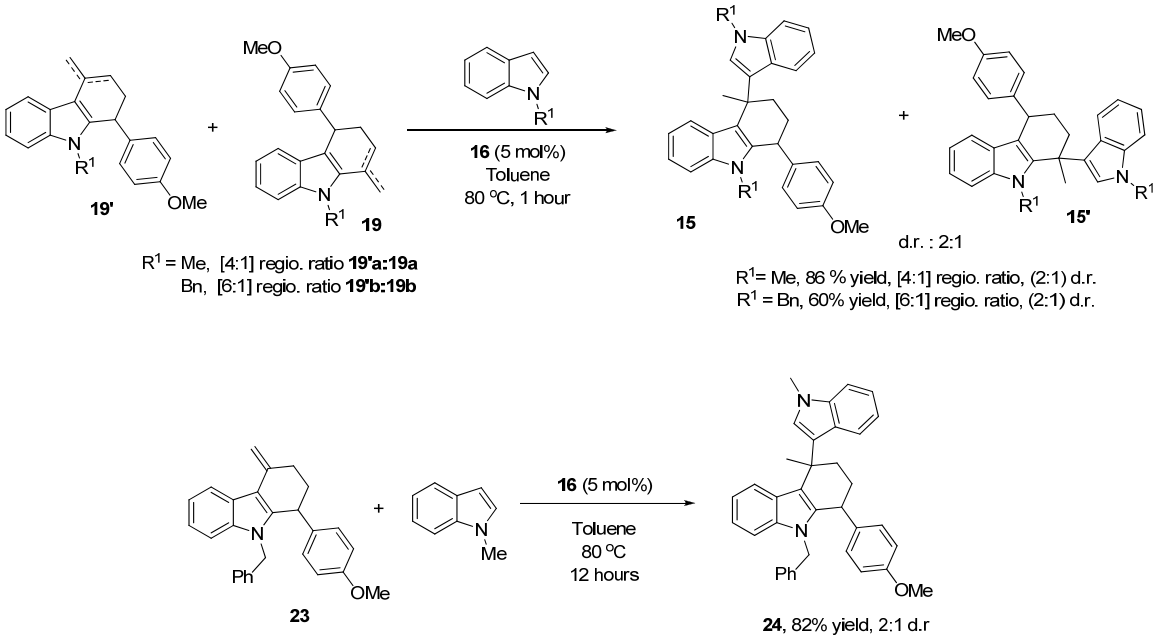
Scheme 14. Gold- and/or acid-catalyzed synthesis of tetrahydrocarbazoles **15** and **15'**



Further evidences for the need of gold and acid in the success of this mechanistic pathway were obtained with the following experiments (Scheme 15). A 4:1 regioisomeric mixture of intermediates **19** and **19'** was submitted with one equivalent of methyl indole in the presence of catalytic amounts of the gold catalyst. Heating up the reaction in toluene for 12 hours afforded a 4:1 regioisomeric mixture of the desired products **15** and **15'**. The selectivity observed in this transformation as well as the regioselectivy observed in the formation of intermediates **19** and **19'** (Scheme 12) are in agreement with the results observed for the reaction with methyl indole and the corresponding 1-cyclopropyl alkyne under the standard reactions conditions (Table 1, entry 8). The same regioselective pattern was observed for intermediates **19** and **19'**, bearing a benzyl group at the nitrogen atom of the indole, affording a 6:1 regioisomeric mixture of

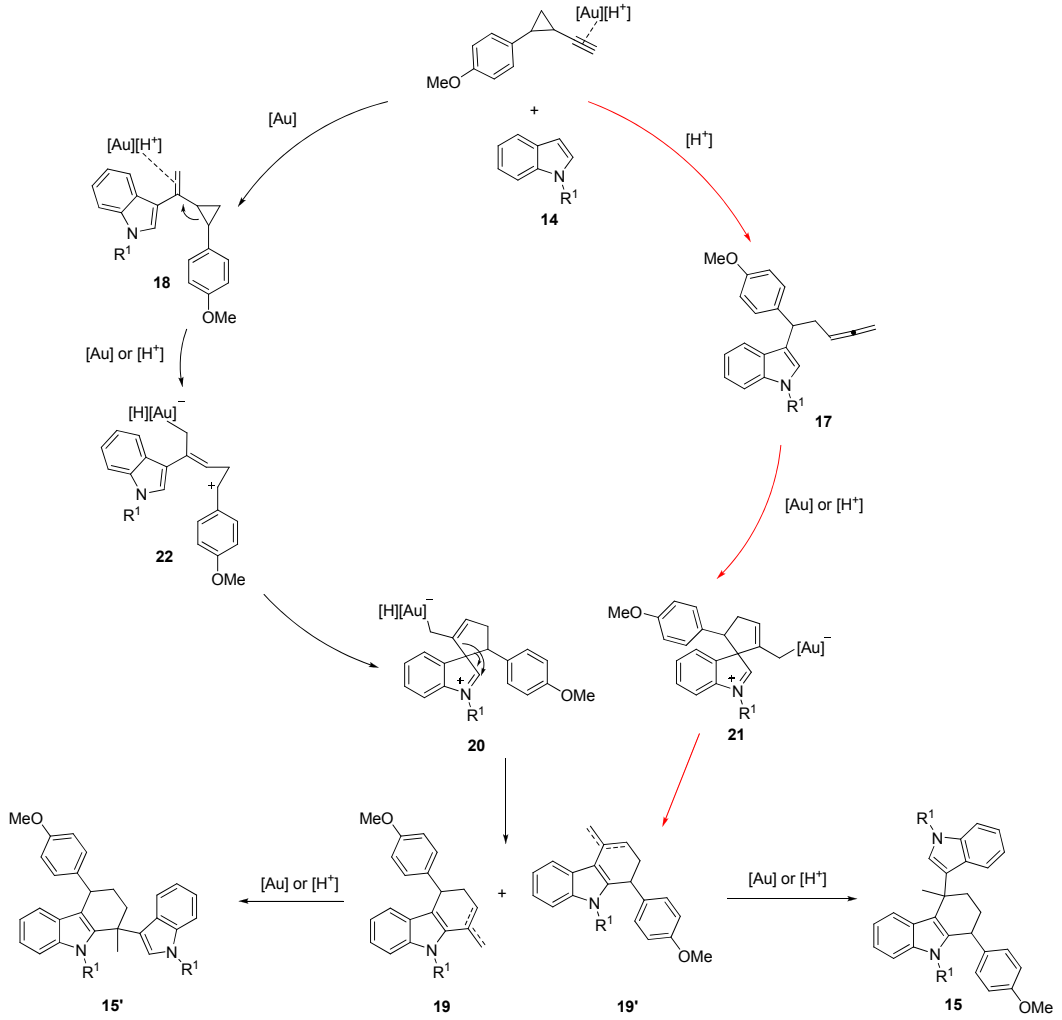
tetrahydrocarbazoles **15** and **15'**. Moreover, the reaction of intermediate **23**, which was previously synthesized, in presence of one equivalent of methyl indole afforded the tetrahydrocabazol **24** in 82% yield as a single regioisomer.

Scheme 15. Gold-catalyzed reaction of carbazoles **19** and **19'**



In summary, a complete mechanistic picture can be formulated using the above collected datas (Scheme 16). We propose a mechanism that involves three main steps. In the first step, both gold and acid catalyzed the formation of intermediates **17** and **18** in a divergent process. Gold-coordination of the alkyne in 1-(2-ethynylcyclopropyl)-4-methoxybenzene triggers the nucleophilic attack of the C3 of the indole delivering intermediate **18**. Furthermore, intermediate **18** can be influenced by the presence of gold or acid. After gold- or acid-activation in **18**, that triggers the formation of the 1,5-dipole **22**, spyrocyclic intermediate **20** is formed. The no regioselectivity observed for the ring expansion process affords regioisomeric mixtures of **19** and **19'**. Then, gold- or acid-activation of the double bond in **19** and **19'** followed by the nucleophilic attack of a second molecule of indole afford the corresponding tetrahydrocarbazoles **15** and **15'**. On the other hand, acid can promote the activation of the position 2 of the cyclopropyl ring triggering the nucleophilic attack of the indole onto this position affording allene **17**. Then, after gold activation of the allene **17**, the intramolecular attack of the indole delivers the formation of the spyrocyclic intermediate **21** which selectively isomerizes to form **19'**.

Scheme 16. Mechanistic proposal



5.4 Conclusion

This work deeply describes the reactivity of 1-ethynylcyclopropyl derivates and indoles under gold catalysts. Highly substituted tetrahydrocarbazoles were obtained in good yields. The regioselectivity of the process is remarkable for *N*-protected indoles with ratios between 4:1, for methyl-protected indoles, and 12:1 for benzyl-protected indoles. In contrast, the process seems to be no regioselective for non-protected indoles. Remarkably, as it was shown in Table 2, the reaction in presence of stoichiometric amounts of base improves considerably the regioselectivity of this transformation. We hypothesize that the presence of traces of acid in the reaction mixture plays a drastical role in the selectivity of the cycloisomerization of the spyrocyclic intermediates to form the corresponding tetrahydrocarbazole products. We also found out that the formation of the tetrahydrocarbazole products can be explained *via* gold-catalysis and/or *via* combination of gold- and acid-catalysis. A plausible reaction mechanism, where both gold and acid are involved (Scheme 6), cannot be ruled out based on experimental evidences.

5.5 References

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Chapter 5

Experimental Section

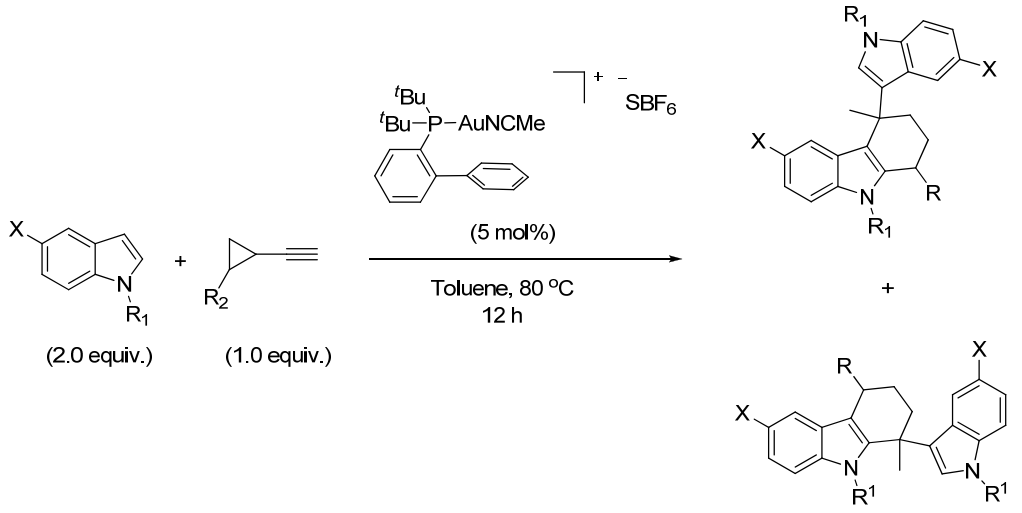
Contents

1. General information

All reactions were carried under non-inert atmosphere. All reagents were used as received unless otherwise noted. Solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silacycle silica gel (230-400 mesh). NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual 1H and 13C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), doublet-doublet-doublet (ddd), quintet (quint), septet (sept), multiplet (m), and broad (br). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer 10 spectra were acquired. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 <l PEG200, 2 <l PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100ml MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard.

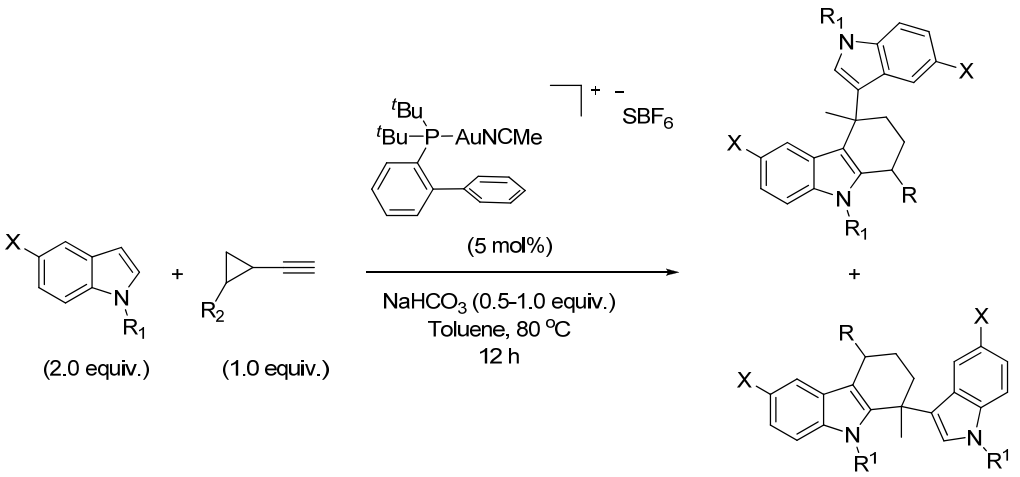
2. Experimental Procedures

2.1 Experimental procedure for tetrahydrocarbazols **15** and **15'**



[{(2-Biphenyl)di-*t*Bu-phosphine}Au(CH_3CN)]SbF_6 (0.0058 mmol, 0.05 equiv.) was added to a solution of the corresponding indol (0.232 mmol, 2.0 equiv.) and the cyclopropyl alkyne (0.116 mmol, 1.0 equiv.) in toluene (0.1M). The mixture was stirred at 80 °C for 12 h. Then, Et_3N (0.05 equiv.) was added to the reaction. The mixture was evaporated in vacuum and the residue was purified by flash chromatography (Hexane:EtOAc) affording the corresponding tetrahydrocarbazol in 42-92% yield.

2.2. Experimental procedure for tetrahydrocarbazols **15** and **15'** with base



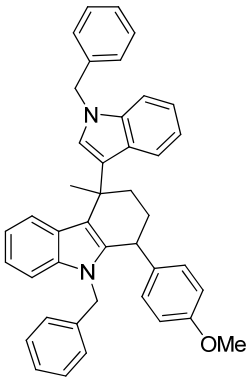
[{(2-Biphenyl)di-*t*Bu-phosphine}Au(CH_3CN)]SbF_6 (0.0058 mmol, 0.05 equiv.) was added to a solution of the corresponding indol (0.232 mmol, 2.0 equiv.), the cyclopropyl alkyne (0.116 mmol, 1.0 equiv.) and $NaHCO_3$ (0.5-1.0 equiv.) in toluene (0.1M). The mixture was stirred at 80 ^oC for 12 h. Then, Et_3N (0.05 equiv.) was added to the reaction. The mixture was evaporated in vacuum and the residue was purified by flash chromatography (Hexane:EtOAc) affording the corresponding tetrahydrocarbazol in 34-83% yield.

2.3. Experimental procedure for allene **17**

TFA (0.186 mmol) was added to a solution of indole (0.232 mmol) and cyclopropyl alkyne (0.232 mmol) in dry toluene (0.1 M). The mixture was heated up to 80 ^oC and stirred until consumption of the starting materials. Then, water was added and extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (Hexane:EtOAc).

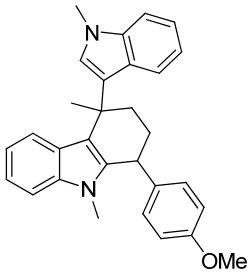
3. Analytical data *N*-protected tetrahydrocarbazoles

9-Benzyl-4-(1-benzyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15a)



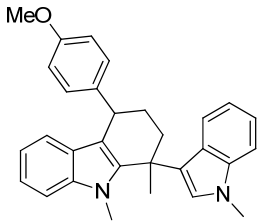
Obtained as 2:1 diastereomeric mixture. Characterization of a 1:0.70 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.1 Hz, 1H, minor isomer), 7.65 (d, *J* = 8.0 Hz, 1H, major isomer), 7.53-7.48 (m, 1H, major and minor isomer), 7.28-6.80 (m, 20H major isomer and 19H minor isomer), 6.68 (d, *J* = 8.7 Hz, 2H, minor isomer), 6.59 (s, 1H, major isomer), 5.31-5.12 (m, 3H, major and minor isomer), 4.76 (d, *J* = 17.0 Hz, 1H, major and minor isomer), 4.02-3.97 (m, 1H, major and minor isomer), 3.80 (s, 3H major isomer), 3.75 (s, 3H, minor isomer), 2.46-2.42 (m, 1H, minor isomer), 2.40-2.34 (m, 1H, major isomer), 2.30-2.20 (m, 1H, minor isomer), 2.14 (s, 3H, major isomer), 2.12-2.07 (m, 1H, major isomer), 2.06 (s, 3H, minor isomer), 2.03-1.99 (m, 1H, minor isomer), 1.96-1.89 (m, 1H, major isomer), 1.83-1.76 (m, 1H, minor isomer), 1.74-1.68 (m, 1H, major isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major and minor isomer): δ = 158.2, 158.1, 138.4, 138.3, 138.1, 137.9, 137.6, 137.5, 137.5, 136.5, 136.4, 136.2, 136.1, 129.1, 128.8, 128.6, 128.6, 128.6, 128.5, 127.8, 127.5, 127.3, 127.2, 127.0, 126.9, 126.5, 126.4, 126.3, 126.0, 125.9, 124.1, 123.3, 121.4, 121.3, 121.2, 121.1, 121.0, 120.9, 120.8, 119.5, 119.3, 118.7, 118.6, 118.4, 113.8, 109.9, 109.8, 109.3, 109.2, 55.2, 55.2, 49.7, 49.6, 46.5, 46.3, 38.9, 38.1, 36.7, 36.4, 34.6, 31.3, 30.4, 29.0, 28.1 ppm (eight carbon are missing due to overlapping); IR (neat, ν/cm^{-1}): 3028, 2929, 2852, 1605, 1507, 1455, 1356, 1321, 1240, 1176, 1037, 835, 736, 695, 562; MS (ESI): m/z (M^+): 609.4.

1-(4-Methoxyphenyl)-4,9-dimethyl-4-(1-methyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15b)



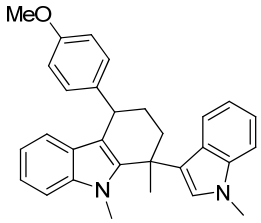
Obtained as 2:1 diastereomeric mixture. Characterization of a 1:0.50 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 1H, major isomer), 7.70 (d, *J* = 7.9 Hz, 1H, minor isomer), 7.54 (d, *J* = 7.9 Hz, 1H, major isomer), 7.42 (d, *J* = 7.9 Hz, 1H, minor isomer), 7.31 (d, *J* = 8.2 Hz, 1H, major isomer), 7.27 (d, *J* = 8.5 Hz, 1H, major isomer), 7.19 (t, *J* = 7.6 Hz, 2H, major isomer), 7.17-7.13 (m, 2H, minor isomer), 7.08-7.05 (m, 1H major isomer and 2H minor isomer), 7.02-6.98 (m, 2H major isomer and 3H minor isomer), 6.94 (t, *J* = 7.5 Hz, 1H, minor isomer), 6.83 (d, *J* = 8.6 Hz, 2H, major isomer), 6.79 (d, *J* = 8.7 Hz, 2H, minor isomer), 6.72 (s, 1H, minor isomer), 6.33 (s, 1H, major isomer), 4.22-4.18 (m, 1H, major and minor isomer), 3.79 (s, 3H, major isomer), 3.76 (s, 3H, minor isomer), 3.67 (s, 3H, minor isomer), 3.58 (s, 3H, major isomer), 3.99 (s, 3H, major isomer), 3.35 (s, 3H, minor isomer), 2.43-2.26 (m, 2H, major isomer), 2.14-2.05 (m, 2H, minor isomer), 2.10 (s, 3H, major isomer), 1.99 (s, 3H, minor isomer), 1.97-1.79 (m, 1H major isomer and 2H minor isomer), 1.73-1.69 (m, 1H, major isomer) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) (major and minor isomer): δ = 158.1, 158.0, 138.0, 137.9, 137.4, 136.8, 136.6, 136.2, 136.1, 129.1, 128.9, 128.8, 127.8, 126.3, 126.1, 125.8, 123.3, 122.3, 121.3, 121.2, 121.1, 121.0, 120.8, 120.7, 120.5, 120.4, 118.8, 118.6, 118.4, 118.3, 118.1, 118.0, 113.9, 113.7, 109.3, 109.2, 108.6, 108.5, 55.2, 39.0, 37.8, 36.8, 36.5, 36.5, 33.9, 32.6, 32.5, 31.2, 29.9, 29.8, 29.4, 29.3, 28.1 ppm; IR (neat, ν/cm^{-1}): 3048, 2921, 2840, 1611, 1509, 1467, 1370, 1244, 1176, 1089, 1031, 907, 835, 731, 562; HRMS (ESI): m/z: calcd for $C_{30}H_{30}N_2NaO^+$: 457.2250, found: 457.2247.

4-(4-Methoxyphenyl)-1,9-dimethyl-1-(1-methyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15'b) minor diastereoisomer



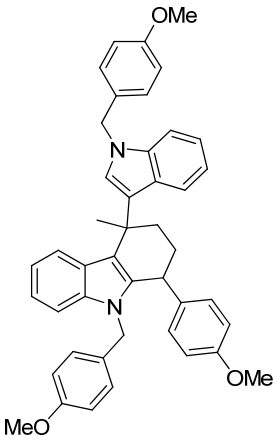
(minor diastereoisomer) Obtained as 2:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.26 (m, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.15-7.12 (m, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.88-6.84 (m, 7H), 4.32 (dd, *J* = 8.2, 5.6 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.30 (bs, 3H), 2.43-2.37 (m, 1H), 2.19-2.12 (m, 1H), 1.98 (s, 3H), 1.93-1.88 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 142.1, 138.7, 137.7, 137.5, 129.2, 126.4, 126.3, 126.0, 125.8, 121.4, 120.5, 120.5, 119.9, 119.0, 118.4, 113.6, 111.6, 109.1, 108.5, 55.2, 40.6, 40.4, 35.8, 32.7, 32.3, 30.7, 26.9 ppm; IR (neat, ν/cm^{-1}): 3043, 2931, 2846, 2249, 1610, 1508, 1468, 1364, 1324, 1240, 1173, 1035, 1015, 906, 829, 727, 647, 567; MS (ESI): m/z $[M+Na]^+$: 457.2.

4-(4-Methoxyphenyl)-1,9-dimethyl-1-(1-methyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15'b) major diastereoisomer



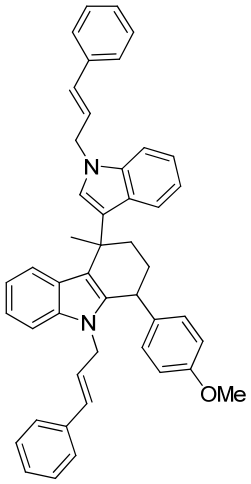
(major diastereoisomer) Obtained as 2:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-6.85 (m, 13H), 4.38-4.34 (m, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.51 (bs, 3H), 2.51-2.46 (m, 1H), 2.39-2.28 (m, 1H), 2.04 (s, 3H), 1.99-1.90 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 142.2, 138.3, 137.6, 137.5, 129.2, 126.7, 126.6, 125.9, 122.0, 121.3, 120.8, 120.7, 119.7, 118.7, 118.7, 113.5, 111.6, 109.2, 108.6, 55.1, 39.9, 36.2, 32.6, 31.3, 30.9, 30.7, 27.2 ppm; IR (neat, ν/cm^{-1}): 3043, 2931, 2846, 2249, 1610, 1508, 1468, 1364, 1324, 1240, 1173, 1035, 1015, 906, 829, 727, 647, 567; MS (ESI): m/z $[M+Na]^+$: 457.2.

9-(4-Methoxybenzyl)-4-(1-(4-methoxybenzyl)-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15d)



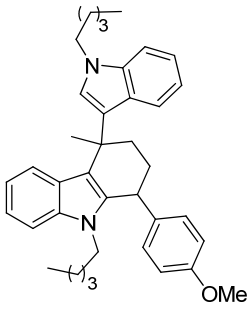
Obtained as 2:1 diastereomeric mixture. Characterization of a 1:0.63 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.2 Hz, 1H, minor isomer), 7.59 (d, *J* = 7.9 Hz, 1H, major isomer), 7.47-7.43 (m, 1H major and minor isomer), 7.22-6.52 (m, 16H major isomer and 13H minor isomer), 6.52 (s, 1H, major isomer), 5.19-5.01 (m, 6H, major and minor isomer), 4.68-4.63 (m, 2H, major and minor isomer), 3.99-3.94 (m, 1H, major and minor isomer), 3.76 (s, 3H, major isomer), 3.72 (s, 3H, minor isomer), 3.71 (s, 3H, major isomer), 3.71 (s, 3H, major isomer), 3.70 (s, 3H, minor isomer), 3.70 (s, 3H, minor isomer), 2.41-2.29 (m, 1H, major and minor isomer), 2.23-2.14 (m, 1H, major isomer), 2.09 (s, 3H, major isomer), 2.06-2.4 (m, 1H, minor isomer), 2.00 (s, 3H, minor isomer), 1.97-1.94 (m, 1H, minor isomer), 1.92-1.88 (m, 1H, major isomer), 1.77-1.64 (m, 2H, major isomer) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) (major and minor isomer): δ = 158.9, 158.8, 158.7, 158.6, 158.2, 158.1, 157.9, 137.5, 137.5, 137.5, 137.4, 136.5, 136.5, 136.2, 136.1, 130.5, 130.3, 130.1, 129.9, 129.1, 128.8, 127.8, 127.7, 127.4, 127.2, 127.1, 126.8, 126.5, 126.4, 126.4, 126.3, 124.0, 123.2, 121.4, 121.3, 121.2, 121.1, 121.0, 120.9, 120.8, 120.7, 119.5, 119.3, 118.6, 118.5, 118.4, 114.1, 114.1, 114.0, 113.9, 113.9, 113.8, 109.9, 109.8, 109.3, 109.2, 55.2, 55.2, 55.1, 49.2, 49.1, 45.9, 45.8, 38.9, 38.1, 36.7, 36.4, 34.6, 31.3, 30.4, 29.7, 29.1, 28.1 ppm; IR (neat, ν/cm^{-1}): 3048, 3002, 2931, 2834, 1610, 1509, 1462, 1353, 1326, 1243, 1173, 1033, 828, 731, 535; HRMS (ESI): m/z: calcd for $C_{44}H_{42}N_2NaO_3^+$: 669.3087, found: 669.3087.

9-Cinnamyl-4-(1-cinnamyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15e)



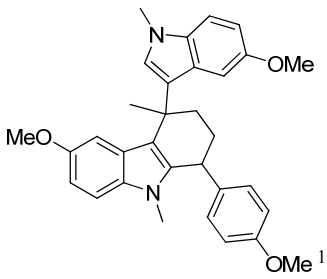
Obtained as 2:1 diastereomeric mixture. Characterization of a 1:0.57 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 1H, minor isomer), 7.74 (d, *J* = 8.0 Hz, 1H, major isomer), 7.55 (d, *J* = 7.9 Hz, 1H, major isomer), 7.50 (d, *J*= 7.9 Hz, 1H, minor isomer), 7.36-6.92 (m, 22H major isomer and 18H minor isomer), 6.84-6.82 (m, 2H major isomer and 1H minor isomer), 6.65 (d, *J* = 8.6 Hz, 2H, minor isomer), 6.51 (s, 1H, major isomer), 6.35-5.87 (m, 4H, major and minor isomer), 4.86-4.63 (m, 3H, major and minor isomer), 4.50-4.39 (m, 1H, major and minor isomer), 4.24 (dd, *J* = 5.4, 2.5 Hz, 1H, major isomer), 4.21 (t, *J* = 6.1 Hz, 1H, minor isomer), 3.74 (s, 3H, major isomer), 3.56 (s, 3H, minor isomer), 2.50-2.38 (m, 1H, major and minor isomer), 2.34-2.27 (m, 1H, minor isomer), 2.20-2.12 (m, 1H, major isomer), 2.15 (s, 3H, major isomer), 2.06 (s, 3H, minor isomer), 2.02-1.94 (m, 1H, major and minor isomer), 1.87-1.80 (m, 1H, minor isomer), 1.77-1.72 (m, 1H, major isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major and minor isomer): 158.2, 158.1, 137.5, 137.4, 137.1, 137.0, 136.7, 136.5, 136.5, 136.4, 136.4, 136.4, 136.2, 136.0, 131.5, 131.3, 131.1, 131.0, 129.4, 129.0, 128.5, 128.5, 128.4, 128.4, 127.9, 127.6, 127.6, 127.5, 127.5, 127.2, 127.2, 126.6, 126.4, 126.4, 126.4, 126.3, 126.3, 126.3, 125.5, 125.4, 125.3, 125.3, 123.9, 122.9, 121.4, 121.3, 121.2, 121.2, 121.0, 120.9, 120.7, 120.7, 119.2, 118.9, 118.6, 118.5, 118.4, 118.3, 113.9, 113.8, 109.8, 109.6, 109.3, 109.2, 55.1, 55.0, 48.0, 47.8, 45.5, 45.0, 39.1, 37.9, 36.7, 36.5, 34.2, 30.1, 29.4, 28.1, 22.3, 14.0 ppm; IR (neat, ν/cm^{-1}): 3056, 3020, 2952, 2932, 2854, 1609, 1509, 1463, 1355, 1327, 1246, 1176, 1032, 965, 908, 833, 733, 692; HRMS (ESI): m/z: calcd for $C_{46}H_{42}N_2NaO^+$: 661.3189, found: 661.3187.

1-(4-Methoxyphenyl)-4-methyl-9-pentyl-4-(1-pentyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15f)



Obtained as 2:1 diastereomeric mixture. Characterization of a 1:1 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.31-7.27 (m, 4H), 7.18-7.11 (m, 4H), 7.07-7.00 (m, 6H), 6.98-6.92 (m, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.78-6.74 (m, 3H), 6.37 (s, 1H), 4.20-4.16 (m, 2H), 4.00 (t, *J* = 7.2 Hz, 2H), 3.94-3.89 (m, 2H), 3.88-3.82 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.73-3.60 (m, 2H), 2.42-2.24 (m, 3H), 2.11 (s, 3H), 2.09-2.02 (m, 1H), 2.00 (s, 3H), 1.92 (dt, *J* = 13.0, 2.1 Hz, 1H), 1.80-1.63 (m, 7H), 1.42-1.06 (m, 20H), 0.87-0.81 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 158.1, 137.2, 137.1, 136.9, 136.8, 136.7, 136.4, 136.3, 135.9, 130.9, 129.2, 128.9, 127.9, 127.2, 126.5, 126.4, 126.2, 126.1, 123.2, 122.6, 122.2, 121.4, 121.3, 121.1, 120.6, 120.5, 120.3, 118.6, 118.4, 118.2, 118.1, 117.9, 117.9, 113.8, 113.7, 109.5, 109.4, 109.1, 109.0, 55.2, 55.2, 47.7, 46.1, 45.9, 43.6, 43.2, 39.2, 38.1, 36.6, 36.5, 34.0, 31.3, 31.3, 30.0, 29.9, 29.9, 29.7, 29.5, 29.4, 29.4, 29.2, 29.1, 29.1, 29.0, 28.1, 22.4, 22.3, 22.291, 22.2, 13.9, 13.9 ppm; IR (neat, ν/cm^{-1}): 3046, 2955, 2929, 2870, 1609, 1509, 1464, 1363, 1327, 1244, 1174, 1104, 1035, 906, 831, 728, 648; HRMS (ESI): m/z: calcd for $C_{38}H_{46}N_2NaO^+$: 569.3502, found: 569.3496.

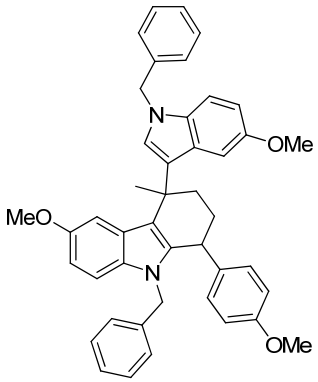
6-Methoxy-4-(5-methoxy-1-methyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4,9-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole (15g)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20-7.15 (m, 3H), 7.01-6.97 (m, 3H), 6.88-6.82 (m, 4H), 6.35 (s, 3H), 4.18-4.17 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.57 (s, 3H), 3.36 (s, 3H), 2.36-2.29 (m, 1H), 2.13-2.05 (m, 1H), 2.07 (s, 3H), 1.86 (dt, *J* = 13.0, 1.65 Hz, 1H), 1.73-1.69 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 153.2, 152.9, 136.9, 136.1, 133.6, 132.9, 129.6, 129.1, 126.6, 126.1, 121.4, 118.2, 113.7, 110.4, 110.2, 109.8,

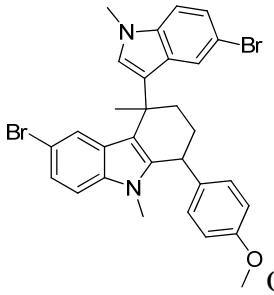
109.1, 103.9, 103.9, 56.1, 56.1, 55.2, 37.9, 36.4, 33.8, 32.6, 29.9, 29.4, 29.1 ppm; IR (neat, ν/cm^{-1}): 2932, 2832, 1614, 1577, 1509, 1484, 1452, 1245, 1213, 1176, 1150, 1040, 910, 837, 790, 727; HRMS (ESI): m/z: calcd for $C_{32}H_{34}rN_2NaO_3^+$: 517.2462, found: 517.2461.

9-Benzyl-4-(1-benzyl-5-methoxy-1*H*-indol-3-yl)-6-methoxy-1-(4-methoxyphenyl)-4-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15h)



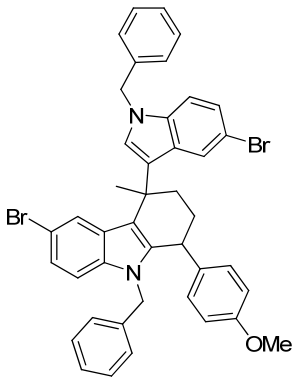
Obtained as 2:1 diastereomeric mixture. Characterization of a 1:0.40 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-6.18 (m, 20H, major and minor isomer), 6.68 (d, *J* = 8.7 Hz, 2H, minor isomer), 6.57 (s, 1H, major isomer), 5.23 (d, *J* = 6.6 Hz, 1H, minor isomer), 5.16 (s, 2H, major isomer), 5.07 (d, *J* = 17.0 Hz, 1H, major and minor isomer), 4.77 (d, *J* = 17.0 Hz, 1H, major isomer), 4.74 (d, *J* = 17.1 Hz, 1H, minor isomer), 4.02 (dd, *J* = 5.4, 2.9 Hz, 1H, major isomer), 3.98 (t, *J* = 5.7 Hz, 1H, minor isomer), 3.80 (s, 3H, major isomer), 3.78 (s, 3H, major isomer), 3.77 (s, 3H, minor isomer), 3.74 (s, 3H, minor isomer), 3.68 (s, 3H, major isomer), 3.62 (s, 3H, minor isomer), 2.43-2.35 (m, 1H, major and minor isomer), 2.30-2.22 (m, 1H, minor isomer), 2.12 (s, 3H, major isomer), 2.10-2.04 (m, 1H, major isomer), 2.03 (s, 3H, minor isomer), 2.01-1.96 (m, 1H, minor isomer), 1.91 (dt, *J* =12.9, 1.9 Hz, 1H, major isomer), 1.82-1.77 (m, 1H, minor isomer), 1.73-1.68 (m, 1H, major isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major and minor isomer): 158.2, 158.1, 153.3, 153.2, 153.1, 138.4, 138.4, 138.2, 138.0, 137.2, 136.9, 136.6, 136.1, 133.0, 132.9, 132.7, 132.6, 129.1, 128.9, 128.8, 128.6, 128.6, 128.5, 128.4, 128.1, 127.3, 127.3, 127.0, 126.9, 126.8, 126.7, 126.6, 126.6, 126.4, 126.3, 125.9, 123.3, 122.3, 119.1, 118.8, 113.8, 113.8, 111.0, 110.7, 110.6, 110.5, 110.4, 110.4, 109.9, 109.8, 104.2, 104.0, 103.5, 103.5, 56.0, 56.0, 55.8, 55.7, 55.2, 55.2, 49.9, 49.8, 46.6, 46.5, 39.0, 38.1, 36.4, 36.3, 34.1, 31.2, 30.2, 29.7, 28.9, 27.7 ppm (two carbon are missing due to overlapping); IR (neat, ν/cm^{-1}): 3054, 3031, 2931, 2829, 1616, 1575, 1509, 1482, 1451, 1353, 1299, 1245, 1215, 1175, 1035, 909, 834, 793, 732, 702; HRMS (ESI): m/z: calcd for $C_{44}H_{42}N_2NaO_3^+$: 669.3087, found: 669.3086.

6-Bromo-4-(5-bromo-1-methyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4,9-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole (15i)



Obtained as 2:1 diastereomeric mixture. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.72 (s, 1H, major isomer), 7.63 (s, 1H, minor isomer), 7.56 (s, 1H, major isomer), 7.30 (s, 1H, minor isomer), 7.25-7.15 (m, 4H, major and minor isomer), 7.09 (d, *J* = 8.3 Hz, 2H, minor isomer), 6.97 (d, *J* = 8.4 Hz, 2H, major isomer), 6.91 (s, 1H, major isomer), 6.89 (s, 1H, minor isomer), 6.84 (d, *J* = 8.4 Hz, 2H, major isomer) 6.39 (s, 1H, major isomer), 4.26-4.21 (m, 1H, major and minor isomer), 3.78 (s, 3H, major isomer), 3.77 (s, 3H, minor isomer), 3.59 (s, 3H, major isomer), 3.37 (s, 3H, minor isomer), 3.35 (s, 3H, major isomer), 2.46-2.39 (m, 1H, minor isomer), 2.31-2.19 (m, 1H, major and minor isomer), 2.11-2.06 (m, 1H, major and minor isomer), 2.03 (s, 3H, major isomer), 1.96-1.89 (m, 1H, major and minor isomer), 1.86 (s, 3H, minor isomer), 1.76-1.71 (m, 1H, major and minor isomer) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) (major and minor isomer): δ = 158.9, 158.8, 138.5, 138.4, 137.3, 137.2, 136.8, 136.7, 136.4, 136.2, 130.3, 129.6, 129.3, 129.1, 128.4, 128.2, 128.1, 124.2, 124.1, 123.8, 123.8, 123.7, 123.6, 123.5, 123.4, 122.8, 122.4, 118.5, 114.7, 114.4, 112.2, 112.1, 112.1, 111.9, 111.5, 111.4, 110.9, 55.7, 38.6, 38.4, 36.7, 36.5, 36.3, 34.9, 33.3, 33.2, 31.1, 30.4, 30.3, 30.1, 29.5, 27.9 ppm; IR (neat, ν/cm^{-1}): 2931, 2855, 1609, 1509, 1469, 1420, 1370, 1245, 1176, 1096, 1035, 986, 907, 788, 730; HRMS (ESI): m/z: calcd for $C_{30}H_{28}Br_2N_2NaO^+$: 613.0457, found: 613.0460.

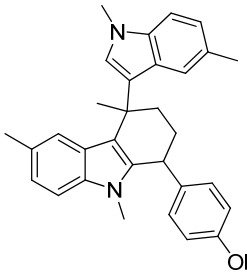
9-Benzyl-4-(1-benzyl-5-bromo-1*H*-indol-3-yl)-6-bromo-1-(4-methoxyphenyl)-4-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15j)



Obtained as 2:1 diastereomeric mixture. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.8 (s, 1H, minor isomer), 7.68 (s, 1H, major isomer), 7.55 (s, 1H, major isomer), 7.48 (s, 1H,

minor isomer), 7.35-7.32 (m, 2H, major and minor isomer), 7.27-6.97 (m, 12H major isomer and 13H minor isomer), 6.85-6.77 (m, 4H, major and minor), 6.66 (s, 1H, major isomer), 5.33-5.19 (m, 2H major and minor isomer), 5.12 (d, J = 17.1 Hz, 1H, minor isomer), 5.07 (d, J = 17.1 Hz, 1H, major isomer), 4.82 (d, J = 17.1 Hz, 1H, minor isomer), 4.73 (d, J = 17.1 Hz, 1H, major isomer), 4.04-4.02 (m, 1H major and minor isomer), 3.82 (s, 3H, major isomer), 3.77 (s, 3H, minor isomer), 2.37-2.29 (m, 2H, major isomer), 2.12-2.09 (m, 2H, minor isomer), 2.06 (s, 3H, major isomer), 1.95 (s, 3H, minor isomer), 1.92-1.81 (m, 1H major isomer and 2H minor isomer), 1.78-1.76 (m, 1H, major isomer) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2) (major and minor isomer): δ = 158.2, 158.1, 137.7, 137.6, 137.5, 137.4, 137.2, 136.1, 136.0, 136.0, 135.6, 135.5, 128.9, 128.9, 128.8, 128.7, 128.6, 128.5, 127.9, 127.8, 127.8, 127.5, 127.4, 127.2, 127.1, 126.2, 126.1, 125.8, 125.7, 124.1, 124.0, 123.8, 123.7, 123.5, 123.3, 122.9, 122.8, 122.6, 118.6, 118.5, 114.1, 113.9, 112.1, 112.0, 111.9, 111.4, 111.3, 110.9, 110.8, 55.2, 55.2, 49.9, 49.9, 46.6, 46.5, 38.2, 38.0, 35.9, 35.8, 35.6, 34.9, 30.5, 28.8, 27.6 ppm; IR (neat, ν/cm^{-1}): 3062, 3028, 2930, 2857, 2835, 1606, 1508, 1463, 1452, 1353, 1245, 1176, 1031, 988, 907, 831, 790, 696; HRMS (ESI): m/z: calcd for $C_{42}H_{36}Br_2N_2NaO^+$: 765.1087, found: 765.1088.

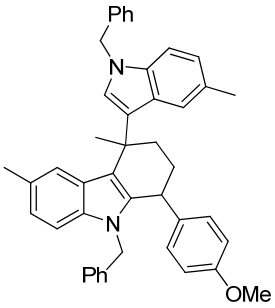
4-(1,5-Dimethyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4,6,9-trimethyl-2,3,4,9-tetrahydro-1*H*-carbazole (15k)



Obtained as 2:1 diastereomeric mixture. Characterization of a 1:0.63 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (s, 1H, major isomer), 7.55 (s, 1H, minor isomer), 7.38 (s, 1H, major isomer), 7.06-6.96 (m, 4H major isomer and 5H minor isomer), 7.22-7.14 (m, 3H major isomer and 2H minor isomer), 6.83-6.78 (m, 2H major and minor isomer), 6.67 (s, 1H, minor isomer), 6.25 (s, 1H, major isomer), 4.18-4.15 (m, 1H, major and minor isomer), 3.79 (s, 3H, major isomer), 3.77 (s, 3H, minor isomer), 3.65 (s, 3H, minor isomer), 3.55 (s, 3H, major isomer), 3.37 (s, 3H, major isomer), 3.30 (s, 3H, minor isomer), 2.48 (s, 3H, major isomer), 2.44 (s, 3H, minor isomer), 2.39 (s, 3H, major isomer), 2.35 (s, 3H, minor isomer), 2.31-2.21 (m, 1H, major and minor isomer), 2.11 (s, 3H, major isomer), 2.09-2.03 (m, 1H, major isomer), 1.99 (s, 3H, minor isomer), 1.96-1.92 (m, 1H, minor isomer), 1.89-1.77 (m, 1H, major and minor isomer), 1.70-1.66 (m, 1H, major isomer) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) (major and minor isomer): δ = 158.1, 158.0, 137.0, 136.8, 136.5, 136.4, 136.3, 136.2, 135.9, 135.8, 129.4, 129.2, 128.8, 128.2, 127.4, 127.3, 127.2, 127.1, 126.5, 126.4, 125.9, 122.7, 122.4, 122.3,

122.0, 121.9, 121.6, 121.2, 121.0, 121.0, 120.8, 118.4, 118.2, 113.9, 113.7, 110.0, 109.1, 108.9, 108.3, 108.2, 55.3, 55.2, 39.3, 39.3, 37.7, 36.9, 36.6, 36.6, 33.5, 32.6, 32.5, 31.4, 30.1, 29.7, 29.5, 29.3, 28.2, 21.7, 21.6, 21.5 ppm; IR (neat, ν/cm^{-1}): 3032, 2929, 2866, 1609, 1508, 1486, 1461, 1371, 1245, 1175, 1092, 1034, 908, 833, 790, 731; HRMS (ESI): m/z: calcd for $C_{22}H_{34}N_2NaO^+$: 485.2563, found: 485.2560.

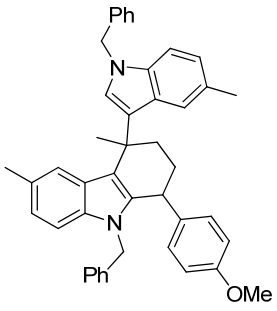
9-Benzyl-4-(1-benzyl-5-methyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4,6-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole (15l) major diastereoisomer



major diastereoisomer

Obtained as 2:1 diastereomeric mixture. ^{1}H NMR (500 MHz, $CDCl_3$)(major diastereoisomer): δ = 7.52 (s, 1H), 7.34 (s, 1H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.20 (d, *J* = 7.1 Hz, 1H), 7.17-7.16 (m, 3H), 7.09 (t, *J* = 7.8 Hz, 2H), 7.0-6.97 (m, 3H), 6.95-6.90 (m, 2H), 6.86-6.84 (m, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.52 (s, 1H), 5.20-5.13 (m, 2H), 5.08 (d, *J* = 17.0 Hz, 1H), 4.74 (d, *J* = 17.0 Hz, 1H), 4.00 (dd, *J* = 5.4, 2.8 Hz, 1H), 3.80 (s, 3H), 2.43 (s, 3H), 2.41-2.34 (m, 1H), 2.34 (s, 3H), 2.13 (s, 3H), 2.10-2.04 (m, 1H), 1.90 (dt, *J* = 13.0, 2.1 Hz, 1H), 1.69-1.65 (m, 1H) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2): 158.2, 138.6, 138.1, 136.2, 136.2, 136.0, 135.8, 129.2, 128.6, 128.6, 128.4, 127.7, 127.5, 127.2, 126.9, 126.7, 126.5, 126.3, 125.9, 122.6, 122.5, 122.3, 121.1, 120.9, 118.8, 113.8, 109.6, 109.0, 55.2, 49.7, 46.3, 37.9, 36.4, 34.2, 30.2, 29.2, 21.7, 21.5 ppm; IR (neat, ν/cm^{-1}): 3056, 3025, 2928, 2858, 1608, 1508, 1495, 1481, 1453, 1372, 1354, 1300, 1246, 1177, 1033, 909, 834, 789, 732, 701; HRMS (ESI): m/z: calcd for $C_{44}H_{42}N_2NaO^+$: 637.3189, found: 637.3192.

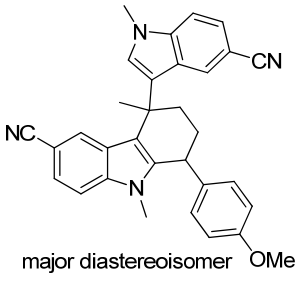
9-Benzyl-4-(1-benzyl-5-methyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4,6-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole (15l) minor diastereoisomer



minor diastereoisomer

Obtained as 2:1 diastereomeric mixture. ^{1}H NMR (500 MHz, $CDCl_3$)(major diastereoisomer): δ = 7.59 (s, 1H), 7.30 (s, 1H), 7.24-6.80 (m, 17H), 6.68 (d, *J* = 8.3 Hz, 2H), 5.23 (dd, *J* = 30.4, 16.5 Hz, 2H), 5.09 (d, *J* = 17.0 Hz, 1H), 4.74 (d, *J* = 17.1 Hz, 1H), 3.97 (t, *J* = 5.8 Hz, 1H), 3.74 (s, 3H), 2.45-2.40 (m, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.28-2.19 (m, 1H), 2.03 (s, 3H), 2.00-1.95 (m, 1H), 1.82-1.77 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 158.0, 138.5, 138.3, 136.6, 136.5, 135.9, 135.9, 128.9, 128.6, 128.5, 127.7, 127.6, 127.4, 127.1, 126.8, 126.6, 126.5, 126.2, 125.9, 123.4, 122.7, 122.2, 121.1, 121.1, 119.1, 113.8, 109.5, 108.9, 55.2, 49.6, 46.5, 38.8, 36.6, 36.4, 31.2, 28.0, 21.5, 21.5 ppm (one carbon is missing due to overlapping); IR (neat, ν/cm^{-1}): 3056, 3025, 2928, 2858, 1608, 1508, 1495, 1481, 1453, 1372, 1354, 1300, 1246, 1177, 1033, 909, 834, 789, 732, 701; HRMS (ESI): m/z: calcd for $C_{44}H_{42}N_2NaO^+$: 637.3189, found: 637.3192.

5-(5-Cyano-1-methyl-1*H*-indol-3-yl)-8-(4-methoxyphenyl)-5,9-dimethyl-6,7,8,9-tetrahydro-5*H*-carbazole-3-carbonitrile (15m) major diastereoisomer

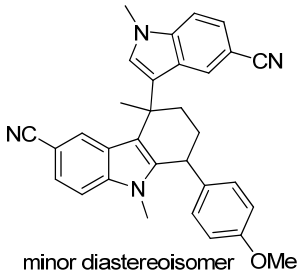


major diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1H), 7.62 (s, 1H), 7.40-7.36 (m, 2H), 7.33-7.30 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.63 (s, 1H), 4.26 (t, *J* = 4.8 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.40 (s, 3H), 2.27-2.22 (m, 1H), 2.18-2.10 (m, 1H), 2.02 (s, 3H), 1.96-1.83 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 139.4, 139.0, 135.2, 129.6, 128.8, 126.3, 125.6, 125.5, 124.1, 123.9, 123.7, 121.1, 121.0, 118.9, 114.2, 110.3, 109.7, 101.5, 101.4, 55.3, 38.3, 35.8, 35.6, 32.9, 30.4, 30.1, 29.1(two carbon missing due to overlapping) ppm; IR (neat, ν/cm^{-1}): 2963, 2926, 2858, 2217, 1609, 1509, 1482, 1375, 1245,

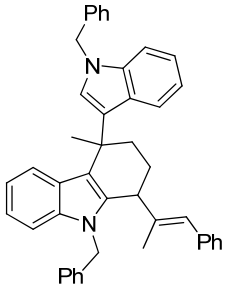
1176, 1091, 1033, 907, 801, 718; HRMS (ESI): m/z: calcd for $C_{32}H_{28}N_4NaO^+$: 507.2155, found: 507.22151.

5-(5-Cyano-1-methyl-1*H*-indol-3-yl)-8-(4-methoxyphenyl)-5,9-dimethyl-6,7,8,9-tetrahydro-5*H*-carbazole-3-carbonitrile (15m) minor diastereoisomer



minor diastereoisomer ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 7.39 (s, 1H), 7.35-7.29 (m, 4H), 7.09-7.07 (m, 3H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.29 (dd, *J* = 5.7. 3.1 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.49 (s, 3H), 2.56-2.48 (m, 1H), 2.32-2.23 (m, 1H), 2.11-2.07 (m, 1H), 1.85 (s, 3H), 1.72-1.68 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 139.3, 138.9, 138.6, 134.6, 128.7, 128.6, 126.5, 125.6, 125.1, 124.3, 124.1, 124.0, 121.2, 120.9, 118.8, 114.4, 110.3, 109.7, 101.4, 101.3, 55.3, 37.3, 37.3, 35.5, 33.1, 30.1, 29.9, 27.4 ppm; IR (neat, ν/cm^{-1}): 2963, 2926, 2858, 2217, 1609, 1509, 1482, 1375, 1245, 1176, 1091, 1033, 907, 801, 718; HRMS (ESI): m/z: calcd for $C_{32}H_{28}N_4NaO^+$: 507.2155, found: 507.22151.

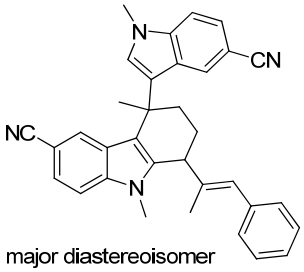
(*E*)-9-Benzyl-4-(1-benzyl-1*H*-indol-3-yl)-4-methyl-1-(1-phenylprop-1-en-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15n)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:0.5 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.0 Hz, 1H, major isomer), 7.63 (d, *J* = 7.5 Hz, 1H, minor isomer), 7.47-7.38 (m, 1H, major and minor isomer), 7.33-6.91 (m, 23H, major and minor isomer), 6.84 (s, 1H, major isomer), 6.61 (s, 1H, minor isomer), 6.24 (s, 1H, major isomer), 6.08 (s, 1H, minor isomer), 5.41-5.16 (m, 4H, major and minor isomer), 3.55 (t, *J* = 5.6 Hz, 1H, major isomer), 3.49-3.47 (m, 1H, minor isomer), 2.61-2.55 (m, 1H, major isomer), 2.48-2.42 (m, 1H, minor isomer), 2.09 (s, 3H, minor isomer), 2.06-2.00 (m, 1H, major isomer), 2.02 (s, 3H, major isomer), 1.95 (s, 3H, minor isomer), 1.92-1.86 (m, 1H, minor isomer), 1.77 (s, 3H, major isomer) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.8, 139.5, 138.5, 138.4, 138.1, 138.0, 137.9, 137.9, 137.6, 137.5, 137.4, 135.8, 135.7, 128.9, 128.8, 128.7, 128.6, 128.6,

128.5, 128.3, 128.2, 128.0, 128.0, 127.9, 127.7, 127.4, 127.3, 127.2, 127.1, 127.0, 126.4, 126.2, 126.1, 126.0, 126.0, 125.8, 125.6, 123.9, 121.4, 121.2, 121.1, 121.1, 120.8, 120.8, 119.7, 119.5, 118.6, 118.4, 109.9, 109.8, 109.3, 109.3, 49.7, 46.6, 43.4, 42.6, 36.6, 36.5, 36.3, 35.2, 29.7, 28.9, 28.2, 28.1, 26.1, 25.4, 17.6, 16.6 ppm (eight carbon are missing due to overlapping); IR (neat, ν/cm^{-1}): 3084, 3047, 3027, 2929, 2857, 1604, 1463, 1453, 1354, 1327, 1178, 1074, 1027, 908, 729, 697; HRMS (ESI): m/z: calcd for $C_{44}H_{40}N_2Na^+$: 619.3083, found: 619.3080.

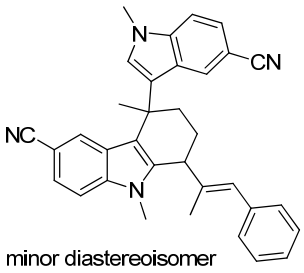
(*E*)-5-(5-Cyano-1-methyl-1*H*-indol-3-yl)-5,9-dimethyl-8-(1-phenylprop-1-en-2-yl)-6,7,8,9-tetrahydro-5*H*-carbazole-3-carbonitrile (15o) major diastereoisomer



major diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (s, 1H), 7.59 (s, 1H), 7.40-7.31 (m, 6H), 7.23-7.22 (m, 3H), 6.63 (s, 1H), 6.01 (s, 1H), 3.75-3.69 (m, 1H), 3.72 (s, 6H), 2.33-2.28 (m, 1H), 2.09-1.94 (m, 3H), 2.01 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.3, 139.0, 138.7, 138.6, 137.6, 129.6, 128.7, 128.3, 128.2, 126.5, 126.3, 125.6, 124.1, 123.9, 123.6, 121.1, 121.0, 119.0, 110.3, 109.6, 101.5, 101.4, 42.5, 35.9, 35.8, 32.9, 29.9, 29.0, 25.2, 17.4 (two carbon missing due to overlapping) ppm; IR (neat, ν/cm^{-1}): 2932, 2858, 2216, 1609, 1482, 1446, 1375 1228, 1139, 1087, 909, 802, 730; HRMS (ESI): m/z: calcd for $C_{34}H_{30}N_4Na^+$: 517.2363, found: 517.2362.

(*E*)-5-(5-Cyano-1-methyl-1*H*-indol-3-yl)-5,9-dimethyl-8-(1-phenylprop-1-en-2-yl)-6,7,8,9-tetrahydro-5*H*-carbazole-3-carbonitrile (15o) minor diastereoisomer

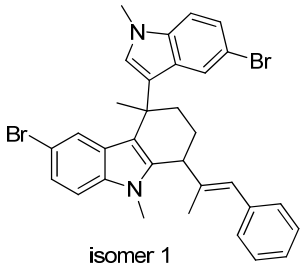


minor diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1H), 7.44 (s, 1H), 7.38-7.30 (m, 6H), 7.24-7.18 (m, 3H), 6.90 (s, 1H), 6.19 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.71-3.68 (m, 1H), 2.43-2.36 (m, 1H), 2.29-2.20 (m, 1H), 2.02-1.95 (m, 1H), 2.00 (s, 3H), 1.87 (s, 3H), 1.85-1.83 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.2, 138.9, 138.8, 138.4, 137.3, 128.9, 128.8, 128.2, 126.6, 126.1, 125.5, 125.4, 125.3, 124.3, 124.1, 124.0, 121.2, 120.8, 119.1, 110.3, 109.7, 101.4, 101.3, 42.4, 36.5, 35.7, 33.0, 29.9, 27.7, 25.4, 17.4 ppm; IR (neat, ν/cm^{-1}): 2933,

2854, 2217, 1728, 1610, 1483, 1447, 1375, 1289, 1234, 1148, 1095, 910, 802, 730, 699; HRMS (ESI): m/z: calcd for $C_{34}H_{30}N_4Na^+$: 517.2363, found: 517.2362.

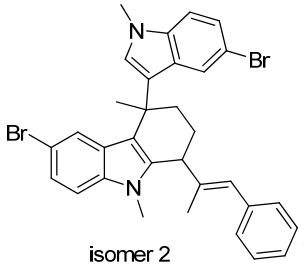
(*E*)-6-Bromo-4-(5-bromo-1-methyl-1*H*-indol-3-yl)-4,9-dimethyl-1-(1-phenylprop-1-en-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15p)



isomer 1

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1H), 7.44 (s, 1H), 7.31-7.27 (m, 2H), 7.24-7.12 (m, 7H), 6.62 (s, 1H), 6.24 (s, 1H), 3.69 (t, *J* = 5.9 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 2.47-2.41 (m, 1H), 2.13-2.06 (m, 1H), 1.93-1.84 (m, 2H), 1.90 (s, 3H), 1.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3Cl): δ = 139.7, 137.8, 137.4, 136.6, 136.2, 128.9, 128.8, 128.0, 127.8, 127.6, 127.4, 126.3, 123.9, 123.5, 123.4, 122.9, 122.6, 118.3, 111.8, 111.7, 110.8, 110.1, 43.5, 36.8, 36.2, 32.8, 29.9, 28.0, 26.1, 16.7 ppm; IR (neat, ν/cm^{-1}): 3020, 2937, 2856, 1737, 1472, 1362, 1281, 1229, 1147, 1095, 1049, 904, 794, 742; HRMS (ESI): m/z: calcd for $C_{32}H_{30}Br_2N_2NaO^+$: 623.0668, found: 623.0662.

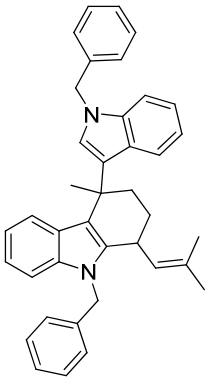
(*E*)-6-Bromo-4-(5-bromo-1-methyl-1*H*-indol-3-yl)-4,9-dimethyl-1-(1-phenylprop-1-en-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15p)



isomer 2

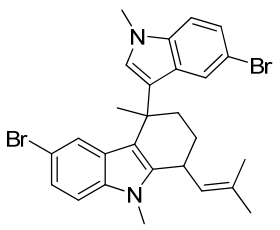
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1H), 7.58 (s, 1H), 7.33-7.27 (m, 3H), 7.25-7.22 (m, 6H), 6.28 (s, 1H), 5.84 (s, 1H), 3.61 (s, 3H), 3.58 (s, 3H), 3.58-3.55 (m, 1H), 2.35-2.31 (m, 1H), 2.08-2.04 (m, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.83-1.80 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3Cl): δ = 138.8, 137.9, 137.5, 136.7, 136.2, 129.8, 128.8, 128.2, 128.1, 127.7, 127.4, 126.3, 123.7, 123.4, 123.3, 123.2, 121.7, 118.1, 111.9, 111.8, 110.9, 110.2, 41.9, 36.3, 34.4, 32.7, 29.4, 29.2, 24.4, 18.0 ppm; IR (neat, ν/cm^{-1}): 3020, 2937, 2856, 1737, 1472, 1362, 1281, 1229, 1147, 1095, 1049, 904, 794, 742; HRMS (ESI): m/z: calcd for $C_{32}H_{30}Br_2N_2NaO^+$: 623.0668, found: 623.0662.

9-Benzyl-4-(1-benzyl-1*H*-indol-3-yl)-4-methyl-1-(2-methylprop-1-enyl)-2,3,4,9-tetrahydro-1*H*-carbazole (15q)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:1 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.31-7.27 (m, 3H), 7.25-7.16 (m, 13H), 7.13-6.96 (m, 11H), 6.94-6.87 (m, 6H), 6.84-6.80 (m, 1H), 6.63 (s, 1H), 5.36-5.15 (m, 10H), 3.72-3.67 (m, 1H), 3.64-3.59 (m, 1H), 2.58 (ddd, *J*= 13.4, 11.1, 2.6 Hz, 1H), 2.48 (ddd, *J* = 13.0, 7.1, 2.4 Hz, 1H), 2.15-2.09 (m, 1H), 2.07 (s, 3H), 2.05-1.96 (m, 1H), 1.95 (s, 3H), 1.92-1.77 (m, 3H), 1.68-1.60 (m, 1H), 1.66 (d, *J* = 1.1 Hz, 3H), 1.63 (d, *J* = 1.1 Hz, 3H), 1.62 (d, *J* = 1.0 Hz, 3H), 1.51 (d, *J* = 1.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.7, 138.6, 138.1, 138.0, 137.9, 137.6, 137.5, 137.4, 137.3, 137.2, 131.6, 131.4, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 127.6, 127.3, 127.3, 127.2, 126.8, 126.7, 126.6, 126.6, 126.5, 126.4, 126.3, 125.8, 125.7, 124.5, 123.6, 121.2, 121.1, 121.0, 121.0, 120.8, 120.5, 120.5, 120.4, 120.4, 118.5, 118.4, 118.3, 118.3, 117.4, 117.3, 109,8, 109.7, 109.1, 109.0, 49.7, 49.6, 46.3, 46.2, 36.8, 36.2, 36.1, 35.9, 32.4, 32.3, 28.6, 28.2, 28.1, 27.5, 25.6, 25.5, 17.8,17.7 ppm; IR (neat, ν/cm^{-1}): 3060, 3025, 2962, 2928, 2857, 1605, 1463, 1452, 1369, 1326, 1178, 1027, 907, 729, 695; HRMS (ESI): m/z: calcd for $C_{39}H_{38}N_2Na^+$: 557.2927, found: 557.2924.

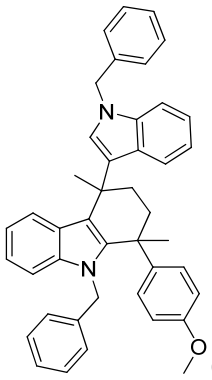
6-Bromo-4-(5-bromo-1-methyl-1*H*-indol-3-yl)-4,9-dimethyl-1-(2-methylprop-1-enyl)-2,3,4,9-tetrahydro-1*H*-carbazole (15r)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:0.45 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 1.7 Hz, 1H, major isomer), 7.59 (d, *J* = 0.8 Hz, 1H, minor isomer), 7.52 (d, *J* = 1.7 Hz, 1H, major isomer), 7.32 (d, *J* = 1.4 Hz, 1H, minor isomer), 7.27 (d, *J* = 1.8 Hz, 1H, minor isomer), 7.25 (d, *J* = 1.8 Hz, 1H, minor

isomer), 7.22 (d, *J* = 1.8 Hz, 1H, minor isomer), 7.20 (d, *J* = 1.8 Hz, 1H, major isomer), 7.16 (s, 1H, major isomer), 7.14-7.11 (m, 2H major isomer and 1H minor isomer), 6.69 (s, 1H, minor isomer), 6.26 (s, 1H, major isomer), 5.37-5.34 (m, 1H, major and minor isomer), 3.81-3.75 (m, 1H, minor isomer), 3.73-3.69 (m, 1H, major isomer), 3.69 (s, 3H, minor isomer), 3.60 (s, 3H, minor isomer), 3.58 (s, 3H, major isomer), 3.57 (s, 3H, major isomer), 2.48-2.42 (m, 1H, minor isomer), 2.35 (ddd, *J* = 13.1, 5.4, 2.3 Hz, 1H, major isomer), 2.10-2.04 (m, 1H, minor isomer), 2.02-1.95 (m, 1H, major isomer), 1.98 (s, 3H, major isomer), 1.85 (s, 3H, minor isomer), 1.83 (d, *J* = 1.1 Hz, 3H, minor isomer), 1.82-1.81 (m, 1H, major isomer), 1.79 (d, *J* = 1.1 Hz, 3H major isomer), 1.77 (bs, 1H, major and minor isomer), 1.74-1.73 (m, 1H, minor isomer), 1.63-1.56 (m, 1H, major and minor isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major and minor isomer): δ = 139.7, 139.2, 136.7, 136.6, 136.1, 135.9, 132.0, 131.9, 129.7, 128.4, 128.4, 128.4, 128.3, 127.9, 127.7, 127.6, 127.4, 126.7, 126.6, 123.7, 123.7, 123.4, 123.3, 123.0, 122.9, 122.5, 122.0, 116.0, 115.9, 111.8, 111.6, 110.8, 110.7, 110.0, 36.9, 36.3, 35.7, 35.4, 32.8, 32.7, 32.6, 31.9, 29.7, 29.7, 29.4, 29.0, 27.8, 27.7, 25.8, 25.8, 17.9, 17.9 ppm (two carbon are missing due to overlapping); IR (neat, ν/cm^{-1}): 2962, 2921, 2852, 1471, 1420, 1370, 1275, 1229, 1141, 1089, 1049, 985, 906, 786, 729, 637, 585; HRMS (ESI): m/z: calcd for $C_{27}H_{28}Br_2N_2Na^+$: 561.0511, found: 561.0506.

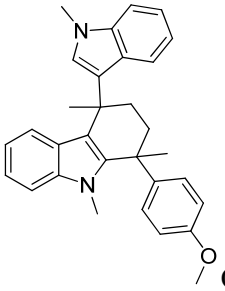
9-Benzyl-4-(1-benzyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1,4-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole (15s)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:0.70 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.8 Hz, 1H, minor isomer), 7.62 (d, *J* = 7.5 Hz, 1H, minor isomer), 7.49 (d, *J* = 7.5 Hz, 1H, major isomer), 7.35-6.83 (m, 21H, major isomer and 17H minor isomer), 6.78 (d, *J* = 6.7 Hz, 2H, minor isomer), 6.70 (s, 1H, major isomer), 6.64 (d, *J* = 8.3 Hz, 2H, minor isomer), 5.38-4.79 (m, 4H, major and minor isomer), 3.82 (s, 3H, major isomer), 3.75 (s, 3H, minor isomer), 2.65-2.53 (m, 1H, major and minor isomer), 2.19 (s, 3H, minor isomer), 2.18-2.13 (m, 1H, minor isomer), 2.06 (s, 3H, major isomer), 2.06-1.99 (m, 1H, major isomer), 1.97-1.89 (m, 1H, major and minor isomer), 1.84-1.79 (m, 1H, major isomer), 1.72-1.68 (m, 1H, minor isomer), 1.67 (s, 3H, major isomer), 1.66 (s, 3H, minor isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (major and minor isomer): 157.9, 157.7, 141.3,

141.1, 140.7, 140.1, 138.4, 138.3, 138.1, 138.0, 137.7, 137.7, 137.6, 137.5, 128.6, 128.6, 128.4, 128.4, 127.6, 127.6, 127.5, 127.3, 127.3, 127.2, 127.2, 127.1, 126.7, 126.6, 126.5, 126.4, 126.4, 126.2, 126.0, 125.8, 125.7, 124.3, 123.3, 121.4, 121.3, 121.2, 121.1, 120.9, 120.8, 120.7, 118.9, 118.7, 118.6, 118.5, 118.4, 118.3, 113.7, 113.7, 109.9, 109.9, 109.8, 109.8, 55.2, 55.1, 49.7, 49.5, 47.6, 47.5, 42.0, 41.8, 40.1, 40.0, 37.4, 36.3, 36.0, 36.0, 29.7, 29.3, 27.9, 25.7 ppm; IR (neat, ν/cm^{-1}): 3056, 3025, 2963, 2928, 2854, 1606, 1509, 1463, 1350, 1327, 1299, 1245, 1181, 1074, 1029, 908, 828, 730, 696; HRMS (ESI): m/z: calcd for $C_{43}H_{40}N_2NaO^+$: 623.3033, found: 623.3032.

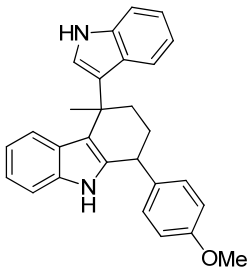
1-(4-Methoxyphenyl)-1,4,9-trimethyl-4-(1-methyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15t)



Obtained as 2:1 diastereomeric mixture. Characterization of a 1.5:1 diastereomeric ratio ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.0 Hz, 1H, minor isomer), 7.55 (d, *J* = 8.0 Hz, 1H, minor isomer), 7.53-7.51 (m, 1H, major isomer), 7.37 (d, *J* = 7.9 Hz, major isomer), 7.28-7.25 (m, XH), 7.21-7.05 (m, xH), 7.02-6.95 (m, 2H), 6.93-6.89 (m, 1H), 6.84 (d, *J* = 8.8 Hz, 2H, major isomer), 6.78 (d, *J* = 8.8 Hz, 2H, minor isomer), 6.62 (s, 1H, major isomer), 6.52 (s, 1H, minor isomer), 3.81 (s, 3H, major isomer), 3.77 (s, 3H, minor isomer), 3.67 (s, 3H, major isomer), 3.62 (s, 3H, minor isomer), 3.36 (s, 3H, major isomer), 3.24 (s, 3H, minor isomer), 2.59-2.54 (m, 1H, major isomer), 2.43-2.37 (m, 1H, major isomer), 2.14-2.07 (m, 1H, minor isomer), 2.09 (s, 3H, minor isomer), 2.03 (s, 3H, major isomer), 1.95-1.65 (m, 1H major isomer and 3H minor isomer), 1.86 (s, 3H, major isomer), 1.85 (s, 3H, minor isomer) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) (major and minor isomer): δ = 157.8, 157.6, 141.4, 141.1, 140.5, 140.3, 138.1, 137.9, 137.8, 137.7, 128.8, 127.9, 127.6, 127.2, 127.2, 126.1, 126.0, 126.0, 125.7, 122.9, 122.6, 121.4, 121.1, 121.0, 120.9, 120.8, 120.8, 120.5, 118.4, 118.4, 118.3, 118.1, 118.1, 117.8, 113.7, 113.6, 109.3, 109.2, 108.5, 108.4, 55.2, 55.1, 41.6, 41.2, 39.9, 37.1, 36.5, 36.1, 35.8, 32.5, 32.5, 31.6, 31.1, 29.4, 28.7, 28.7, 28.7, 25.1 ppm; IR (neat, ν/cm^{-1}): 3051, 2963, 2930, 2837, 2358, 1744, 1608, 1509, 1468, 1371, 1326 1247, 1180, 1094, 1032, 908, 828; HRMS (ESI): m/z: calcd for $C_{31}H_{32}N_2NaO^+$: 471.2406, found: 471.2409.

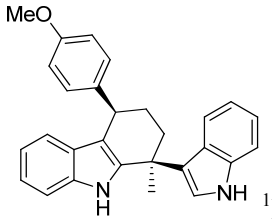
4. Analytical data non-protected tetrahydrocarbazoles

4-(1*H*-Indol-3-yl)-1-(4-methoxyphenyl)-4-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15c)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1: 0.81 diastereomeric ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.0 Hz, 1H, major isomer), 7.85 (s, 1H, minor isomer), 7.78 (s, 1H, major isomer), 7.52 (d, *J* = 8.0 Hz, 1H, major isomer), 7.49 (d, *J* = 8.6 Hz, 2H, minor isomer), 7.40-6.81 (m, 9H major isomer and 12H minor isomer), 6.60 (d, *J* = 2.3 Hz, 1H, major isomer), 4.25-4.22 (m, 1H, minor isomer), 4.10 (dd, *J* = 10.5, 5.7 Hz, 1H, major isomer), 3.84 (s, 3H, minor isomer), 3.80 (s, 3H, major isomer), 2.73-2.69 (m, 1H, major isomer), 2.53-2.48 (m, 1H, minor isomer), 2.22-2.15 (m, 1H, major isomer), 2.12 (s, 3H, major isomer), 2.04 (s, 3H, minor isomer), 2.02-1.97 (m, 1H major isomer and 3H minor isomer), 1.80-1.71 (m, 1H, major isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (2x), 137.4, 137.2, 136.6, 136.2, 136.1, 136.0, 135.9, 135.4, 129.3, 129.2, 127.3, 126.9, 126.8, 125.930, 125.4, 125.0, 124.3, 124.2, 121.9, 121.3, 121.3, 121.0, 120.9, 120.9, 120.8, 120.3, 118.9, 118.8, 118.7, 118.7, 118.5, 114.1, 114.0, 111.4, 111.1, 110.6, 110.5, 55.3, 55.2, 41.7, 40.7, 38.6, 37.6, 36.8, 35.6, 30.9, 30.7, 28.8, 27.7 (one carbon missing due to overlapping) ppm; IR (neat, ν/cm^{-1}): 3408, 3054, 2933, 2846, 1611, 1509, 1455, 1304, 1240, 1175, 1101, 1031, 1013, 906, 830, 728; HRMS (ESI): m/z: calcd for $C_{28}H_{26}N_2NaO^+$: 429.1937, found: 429.1935.

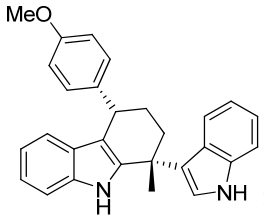
1-(1*H*-Indol-3-yl)-4-(4-methoxyphenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15'c)



^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.78 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.18-7.16 (m, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.88-6.82 (m, 2H), 6.75-7.72 (m, 3H), 4.15 (t, *J* = 6.7 Hz, 1H), 3.70 (s, 3H), 2.52-2.47 (m, 1H), 2.16-2.11 (m, 1H), 1.88-1.83 (m, 1H), 1.85 (s, 3H), 1.78-1.72 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.8, 141.4, 138.3, 137.1, 135.9, 129.1, 127.3, 125.2, 123.6, 122.8, 121.8, 121.2, 120.7, 119.9, 119.3, 119.0, 113.6, 112.0, 111.4, 110.6, 55.2, 39.3, 36.9, 36.2, 31.4, 27.7 ppm; IR (neat, ν/cm^{-1}): 3400, 3051, 2926, 2854, 1614,

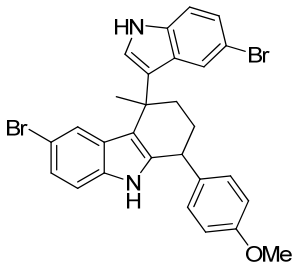
1508, 1457, 1332, 1306, 1240, 1175, 1103, 1031, 1012, 831, 735; HRMS (ESI): m/z: calcd for $C_{28}H_{26}N_2NaO^+$: 429.1937, found: 429.1936.

1-(1*H*-Indol-3-yl)-4-(4-methoxyphenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15'c)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1H), 7.64 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.16-7.08 (m, 3H), 7.04-7.01 (m, 2H), 6.92-6.84 (m, 5H), 4.33 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.83 (s, 3H), 2.57-2.50 (m, 1H), 2.27-2.19 (m, 1H), 2.06-1.90 (m, 2H), 1.95 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.9, 141.9, 138.5, 136.9, 135.9, 129.0, 127.2, 125.5, 123.4, 121.9, 121.8, 120.9, 120.5, 119.9, 119.6, 118.8, 113.7, 111.7, 111.2, 110.6, 55.2, 39.9, 37.6, 35.6, 32.3, 27.6 ppm; IR (neat, ν/cm^{-1}): 3405, 3051, 2926, 2854, 1614, 1508, 1455, 1327, 1265, 1240, 1175, 1103, 1030, 1011, 835, 739; HRMS (ESI): m/z: calcd for $C_{28}H_{26}N_2NaO^+$: 429.1937, found: 429.1936.

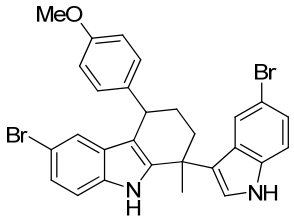
6-Bromo-4-(5-bromo-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15u)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:0.76 ratio of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (bs, 1H, minor isomer), 7.91 (s, 1H, major isomer), 7.88 (bs, 1H, major isomer), 7.56 (d, *J* = 1.3 Hz, 1H, major isomer), 7.54 (d, *J* = 7.5 Hz, 2H, minor isomer), 7.41 (s, 1H, minor isomer), 7.28-7.04 (m, 7H major isomer, 9H minor isomer) , 6.98 (d, *J* = 2.0 Hz, 1H, minor isomer), 6.91 (d, *J* = 8.6 Hz, 2H, minor isomer), 6.86 (d, *J* = 8.6 Hz, 2H, major isomer), 6.62 (d, *J* = 2.3 Hz, 1H, major isomer), 4.22 (dd, *J* = 8.0, 5.7 Hz, 1H, minor isomer), 4.08 (dd, *J* = 10.2, 5.5 Hz, 1H, major isomer), 3.83 (s, 3H, minor isomer), 3.79 (s, 3H, major isomer), 2.61-2.57 (m, 1H, major isomer), 2.46-2.39 (m, 1H, minor isomer), 2.20-2.13 (m, 1H, major isomer), 2.06-1.94 (m, 1H major isomer, 3H minor isomer), 2.02 (s, 3H, major isomer), 1.96 (s, 3H, minor isomer), 177-1.68 (m, 1H, major isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 158.6, 138.0, 137.0, 136.0, 135.9, 135.4, 135.3, 134.7, 134.7, 129.3, 129.1, 128.5, 128.3, 127.5, 127.1, 124.9, 124.4, 124.4, 124.4, 123.9, 123.8, 123.8,

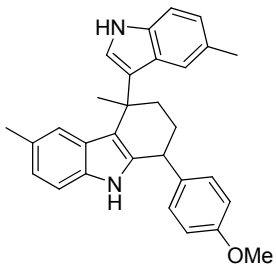
123.4, 123.1, 123.1, 123.0, 122.4, 118.0, 117.9, 114.3, 114.2, 112.8, 112.7, 112.3, 112.3, 112.2, 112.1, 112.0, 55.3, 55.3, 41.5, 40.7, 38.5, 37.7, 36.4, 35.4, 30.7, 30.4, 28.7, 27.5 ppm (one carbon missing due to overlapping); IR (neat, ν/cm^{-1}): 3420, 2962, 2933, 2852, 1605, 1507, 1455, 1310, 1235, 1170, 1025, 910, 800, 730; HRMS (ESI): m/z: calcd for $C_{28}H_{24}Br_2N_2NaO^+$: 585.0147, found: 585.0140.

6-Bromo-1-(5-bromo-1*H*-indol-3-yl)-4-(4-methoxyphenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (15'u)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:1 ratio of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (bs, 2H), 7.83 (s, 1H), 7.71 (s, 1H), 7.65 (s, 1H), 7.28 (s, 1H), 7.25-7.21 (m, 4H), 7.19-7.10 (m, 8H), 7.05-7.01 (m, 2H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.87-6.85 (m, 5H), 4.26 (t, *J* = 6.5 Hz, 1H), 4.20 (t, *J* = 6.0 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.50-2.45 (m, 1H), 2.43-2.36 (m, 1H), 2.30-2.23 (m, 1H), 2.20-2.14 (m, 1H), 1.94-1.80 (m, 4H), 1.91 (s, 3H), 1.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 157.9, 142.6, 142.4, 137.6, 137.3, 135.7, 135.6, 134.6, 134.5, 129.2, 128.9, 128.9, 127.0, 126.8, 125.0, 124.9, 124.2, 124.0, 123.8, 123.3, 123.1, 122.9, 122.8, 122.7, 122.3, 122.2, 113.9, 113.8, 112.8, 112.8, 112.7, 112.7, 112.4, 112.3, 112.1, 112.0, 111.7, 111.6, 55.2, 55.2, 38.9, 38.4, 36.5, 36.1, 36.0, 35.7, 31.6, 31.0, 27.6, 27.4 ppm (one carbon missing due to overlapping); IR (neat, ν/cm^{-1}): 3425, 2933, 2846, 1605, 1508, 1461, 1298, 1240, 1175, 1106, 1031, 905, 795, 727, 581; HRMS (ESI): m/z: calcd for $C_{28}H_{24}Br_2N_2NaO^+$: 585.0147, found: 585.0139.

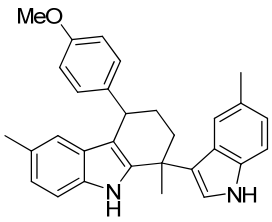
1-(4-Methoxyphenyl)-4,6-dimethyl-4-(5-methyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15v)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:0.78 ratio of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (bs, 1H, minor isomer), 7.71 (bs, 1H, major isomer), 7.68 (s, 1H, major isomer), 7.43 (s, 1H, minor isomer), 7.36 (s, 1H major, 1H minor), 7.31 (s, 1H, major isomer), 7.24 (s, 1H, major isomer), 7.22 (s, 1H, minor isomer), 7.13-

7.08 (m, 3H major isomer and 4H minor isomer), 7.03-6.82 (m, 4H major isomer and 3H minor isomer), 6.75 (d, *J* = 1.7 Hz, 1H, minor isomer), 6.57 (d, *J* = 2.2 Hz, 1H, major isomer), 4.18 (t, *J* = 6.0 Hz, 1H, minor isomer), 4.07 (dd, *J* = 10.6, 5.6 Hz, 1H, major isomer), 3.82 (s, 3H, minor isomer), 3.79 (s, 3H, major isomer), 2.70-2.66 (m, 1H, major isomer), 2.50 (s, 3H, major isomer), 2.46-2.42 (m, 1H, minor isomer), 2.39 (s, 3H, minor isomer), 2.34 (s, 3H, major isomer), 2.29 (s, 3H, minor isomer), 2.18-2.08 (m, 1H, major isomer), 2.10 (s, 3H, major isomer), 2.05 (s, 3H, minor isomer), 2.04-1-86 (m, 1H major and 3H minor), 1.78-1.69 (m, 1H, major isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 158.4, 136.7, 136.2, 136.1, 135.8, 135.6, 135.4, 134.5, 134.5, 129.3, 129.2, 129.0, 128.2, 127.9, 127.9, 127.7, 127.7, 127.1, 127.0, 126.0, 125.6, 124.6, 124.1, 123.7, 122.9, 122.4, 122.3, 120.8, 120.7, 120.6, 120.5, 118.6, 118.1, 114.0, 113.9, 111.0, 110.8, 110.2, 110.1, 55.3, 55.2, 41.8, 40.2, 38.5, 36.7, 36.6, 35.9, 30.7, 30.5, 29.7, 28.7, 27.9, 21.7, 21.5, 21.5 ppm; IR (neat, ν/cm^{-1}): 3408, 2962, 2927, 2857, 1507, 1460, 1298, 1240, 1164, 1031, 921, 806, 732, 419; HRMS (ESI): m/z: calcd for $C_{30}H_{30}N_2NaO^+$: 457.2250, found: 457.2252.

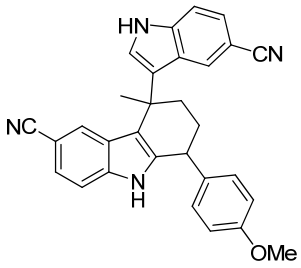
4-(4-Methoxyphenyl)-1,6-dimethyl-1-(5-methyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (15'v)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:0.57 ratio of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (bs, 2H major and minor isomer), 7.72 (s, 1H, minor isomer), 7.62 (s, 1H, major isomer), 7.34 (s, 1H, minor isomer), 7.25-7.21(m, 1H major isomer and 2H minor isomer), 7.19 (d, *J* = 8.5 Hz, 2H, major isomer), 7.14 (d, *J* = 8.2 Hz, 1H, minor isomer), 7.08 (d, *J* = 8.2 Hz, 1H, major isomer), 7.05 (s, 1H, major isomer), 7.00-6.95 (m, 1H, minor isomer), 6.97 (dd, *J* = 8.3, 1.2 Hz, 1H major), 6.91 (dd, *J* = 8.2, 1.2 Hz, 1H, minor isomer) 6.88 (s, 1H, minor isomer), 6.78 (s, 1H, minor isomer), 6.88-6.82 (m, 3H major isomer and 5H minor isomer), 6.69 (s, 1H, major isomer), 4.28 (t, *J* = 6.3 Hz, 1H, major isomer), 4.23 (t, *J* = 6.0 Hz, 1H, minor isomer), 3.82 (s, 3H, major isomer), 3.79 (s, 3H, minor isomer), 2.59-2.53 (m, 1H, minor isomer), 2.50-2.45 (m, 1H major isomer and minor isomer), 2.36 (s, 3H, minor isomer), 2.30 (s, 3H, major isomer), 2.29 (s, 3H, minor isomer), 2.27 (s, 3H, major isomer), 2.22-2.14 (m, 1H major and minor isomer), 1.94-1.83 (m, 2H major isomer, 1H minor isomer), 1.92 (s, 3H, major isomer), 1.88 (s, 3H, minor isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 157.6, 142.1, 141.8, 138.5, 138.2, 135.4, 135.3, 134.2, 134.1, 129.1, 129.0, 128.5, 128.3, 128.2, 127.9, 127.7, 127.4, 125.6, 125.4, 123.5, 123.4, 122.9, 122.8, 122.7, 122.6, 122.5, 122.4, 120.5,

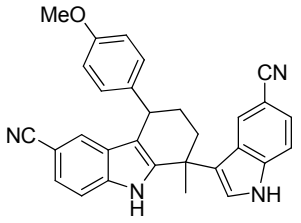
120.2, 119.4, 119.4, 113.5, 113.5, 111.0, 110.9, 110.9, 110.8, 110.3, 110.2, 55.2, 55.2, 39.1, 38.5, 36.2, 36.1, 35.9, 35.8, 31.8, 31.1, 27.9, 27.5, 21.7, 21.5, 21.4, 21.4 ppm; IR (neat, ν/cm^{-1}): 3405, 2927, 2846, 1611, 1509, 1460, 1300, 1243, 1174, 1031, 908, 795, 732; HRMS (ESI): m/z: calcd for $C_{30}H_{30}N_2NaO^+$: 457.2250, found: 457.2249.

5-(5-Cyano-1*H*-indol-3-yl)-8-(4-methoxyphenyl)-5-methyl-6,7,8,9-tetrahydro-5*H*-carbazole-3-carbonitrile (15w)



Obtained as 1:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1H), 8.49 (s, 1H), 8.09 (s, 1H), 8.05 (s, 1H), 7.97 (s, 1H), 7.73 (s, 1H), 7.49-7.34 (m, 8H), 7.31 (s, 1H), 7.28 (d, *J* = 5.4 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 1H), 4.36 (dd, *J* = 10.1, 5.6 Hz, 1H), 4.20 (dd, *J* = 8.7, 5.8 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.61-2.58 (m, 1H), 2.55-2.50 (m, 1H), 2.33-2.30 (m, 1H), 2.23-2.16 (m, 2H), 2.10-2.00 (m, 2H), 2.06 (s, 3H), 2.00 (s, 3H), 1.85 (dd, *J* = 22.2, 10.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 158.7, 139.0, 138.8, 138.3, 137.8, 137.6, 134.6, 134.5, 129.3, 129.0, 129.0, 128.2, 126.4, 126.3, 126.1, 125.8, 125.7, 125.6, 125.4, 125.1, 125.0, 124.9, 124.7, 124.6, 124.5, 124.3, 124.2, 123.1, 121.0, 120.9, 120.9, 118.5, 118.4, 114.4, 114.3, 112.4, 112.3, 111.6, 111.5, 102.0, 102.0, 101.8, 101.6, 55.3, 55.3, 41.2, 40.7, 39.0, 38.1, 36.1, 34.9, 31.0, 30.0, 28.6, 27.2, ppm; IR (neat, ν/cm^{-1}): 3316, 2927, 2852, 2218, 1613, 1509, 1469, 1339, 1310, 1245, 1177, 1033, 908, 807, 731, 647; HRMS (ESI): m/z: calcd for $C_{30}H_{24}N_4NaO^+$: 479.1842, found: 479.1845.

8-(5-Cyano-1*H*-indol-3-yl)-5-(4-methoxyphenyl)-8-methyl-6,7,8,9-tetrahydro-5*H*-carbazole-3-carbonitrile (15'w)

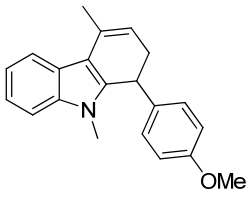


Obtained as 1:1 diastereomeric mixture. Characterization of a 1:0.79 ratio of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1H, minor isomer), 8.42 (s, 1H, major isomer), 8.19 (s, 1H, major isomer), 7.91 (s, 1H major and minor), 7.43-7.24 (m, 4H major isomer and 6H minor isomer), 7.21 (d, *J* = 2.1 Hz, 1H, minor isomer), 7.17-7.15 (m, 3H,

major isomer), 7.12 (d, *J* = 8.5 Hz, 2H, major isomer), 6.94 (d, *J* = 2.2 Hz, 1H, major isomer), 6.89-6.86 (m, 4H, minor isomer), 4.32 (dd, *J* = 8.4, 5.9 Hz, 1H, minor isomer), 4.23 (t, *J* = 6.52, 1H, major isomer), 3.84 (s, 3H, minor isomer), 3.80 (s, 3H, major isomer), 2.51-2.41 (m, 2H, major isomer), 2.30-2.19 (m, 2H, major isomer), 2.04-1.93 (m, 2H, minor isomer), 1.95 (s, 3H, minor isomer), 1.92 (s, 3H, major isomer), 1.87-1.79 (m, 2H, minor isomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 158.2, 143.0, 142.9, 141.6, 141.5, 141.3, 138.8, 138.7, 137.7, 137.6, 136.9, 136.5, 128.8, 128.7, 127.2, 126.8, 126.1, 125.7, 125.6, 125.3, 125.2, 125.1, 124.9, 124.8, 124.7, 124.6, 124.1, 123.9, 123.7, 120.9, 120.8, 120.4, 114.1, 113.3, 113.2, 112.4, 112.3, 111.5, 111.3, 102.9, 102.7, 102.4, 102.2, 55.2, 39.6, 38.5, 37.6, 36.4, 36.2, 35.5, 31.9, 30.9, 27.4, 27.4 ppm; IR (neat, ν/cm^{-1}): 3321, 2926, 2857, 2218, 1614, 1509, 1471, 1244, 1176, 1031, 907, 806, 730; HRMS (ESI): m/z: calcd for $C_{30}H_{24}N_4NaO^+$: 479.1842, found: 479.1840.

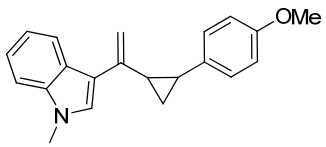
5. Analytical data intermediates:

1-(4-Methoxyphenyl)-4,9-dimethyl-2,9-dihydro-1*H*-carbazole



^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.29 (d, *J* = 8.3 Hz, 1H), 7.17-7.15 (m, 2H), 7.10 (ddd, *J* = 8.2, 6.6, 1.5 Hz, 1H), 6.94-6.87 (m, 1H), 6.81-6.79 (m, 2H), 5.68 (dt, *J* = 4.8, 1.6 Hz, 1H), 4.22 (t, *J* = 8.0 Hz, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 7.79-7.71 (m, 1H), 2.57-2.49 (m, 1H), 2.32 (d, *J* = 1.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 158.8, 138.8, 137.7, 137.2, 129.3, 129.3, 127.9, 126.3, 124.7, 121.6, 119.7, 119.4, 114.1, 109.6, 55.7, 38.3, 34.9, 32.6, 21.2 ppm; IR (neat, ν/cm^{-1}): 3051, 2999, 2929, 2858, 2837, 1609, 1508, 1461, 1451, 1365, 1301, 1240, 1175, 1033, 829, 738, 549; HRMS (ESI): m/z: calcd for $C_{21}H_{21}NNaO^+$: 326.1515, found: 326.1512.

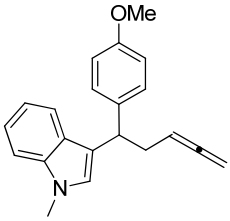
3-(1-(2-(4-Methoxyphenyl)cyclopropyl)vinyl)-1-methyl-1*H*-indole (18a)



^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.92 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.18-7.12 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.47 (s, 3H), 5.08 (s, 3H), 3.81 (s, 3H), 3.72 (s, 3H), 2.07-1.97 (m, 2H), 1.47-1.42 (m, 1H), 1.21 (td, *J* = 8.6, 5.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 158.5, 143.2, 138.2, 135.5, 128.5, 127.2,

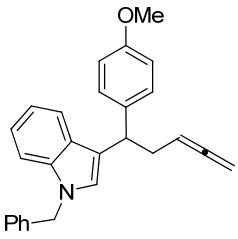
126.5, 122.3, 121.2, 120.3, 117.0, 114.4, 110.0, 106.2, 55.8, 33.3, 29.3, 25.6, 15.5 ppm; IR (neat, ν/cm^{-1}): 3043, 3008, 2927, 2834, 1612, 1512, 1472, 1464, 1244, 1225, 1177, 1103, 1034, 833, 806, 737, 539; HRMS (ESI): m/z: calcd for $C_{21}H_{22}NO^+$: 304.1696, found: 304.1694.

3-(1-(4-Methoxyphenyl)penta-3,4-dienyl)-1-methyl-1*H*-indole (17a)



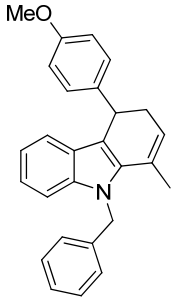
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.38 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.93 (s, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.09 (q, *J* = 7.0 Hz, 1H), 4.66-4.56 (m, 1H), 4.24 (t, *J* = 7.6 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.91-2.83 (m, 1H), 2.74-2.66 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 209.6, 158.6, 137.8, 137.6, 129.4, 127.9, 126.6, 122.000, 119.8, 119.1, 118.7, 114.1, 109.7, 89.1, 74.7, 55.7, 42.7, 35.9, 33.1 ppm; IR (neat, ν/cm^{-1}): 3048, 2991, 2927, 2898, 2834, 1947, 1609, 1509, 1482, 1466, 1327, 1244, 1175, 1034, 841, 738, 550; HRMS (ESI): m/z: calcd for $C_{21}H_{21}NNaO^+$: 326.1515, found: 326.1512.

1-Benzyl-3-(1-(4-methoxyphenyl)penta-3,4-dienyl)-1*H*-indole (17b)



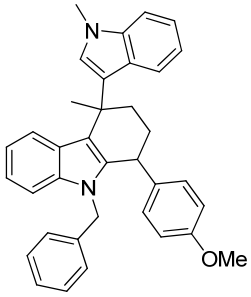
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.9 Hz, 1H), 7.27-7.23 (m, 3H), 7.21-7.16 (m, 3H), 7.09-7.05 (m, 3H), 6.98-6.93 (m, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 5.24 (s, 2H), 5.03 (q, *J* = 7.0 Hz, 1H), 4.52-4.49 (m, 2H), 4.23 (t, *J* = 7.5 Hz, 1H), 3.72 (s, 3H), 2.86-2.78 (m, 1H), 2.69-2.61 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 157.9, 137.8, 136.9, 136.7, 128.9, 128.7, 127.7, 127.5, 126.6, 125.5, 121.7, 119.7, 118.9, 118.9, 113.6, 109.5, 88.6, 74.4, 55.2, 49.9, 42.2, 35.5 ppm; IR (neat, ν/cm^{-1}): 3048, 2991, 2927, 2898, 2834, 1947, 1609, 1509, 1482, 1466, 1327, 1244, 1175, 1034, 841, 738, 550; HRMS (ESI): m/z: calcd for $C_{27}H_{25}NNaO^+$: 402.1828, found: 402.1823.

9-Benzyl-4-(4-methoxyphenyl)-1-methyl-4,9-dihydro-3*H*-carbazole (X)



^{1}H NMR (400 MHz, Toluene-d^{8}): δ = 7.19 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.04-6.94 (m, 5H), 6.80 (d, *J* = 7.0 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 5.44-5.41 (m, 1H), 5.13 (s, 2H), 4.27-4.22 (m, 1H), 3.33 (s, 3H), 2.68-2.48 (m, 2H), 1.91 (d, *J* = 1.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, Toluene-d^{8}): δ = 158.8, 139.2, 138.9, 136.4, 129.2, 127.4, 127.2, 126.8, 125.7, 122.1, 120.3, 120.2, 114.1, 109.7, 54.6, 48.2, 38.9, 35.1 ppm (five carbon are missing due to overlapping); IR (neat, ν/cm^{-1}): 3060, 3025, 2933, 2829, 1608, 1508, 1463, 1452, 1353, 1300, 1245, 1176, 1033, 830, 740; MS (ESI): m/z $[M+1]^{+}$ = 380.2.

9-Benzyl-1-(4-methoxyphenyl)-4-methyl-4-(1-methyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (24)



Obtained as 1:1 diastereomeric mixture. Characterization of a 1:0.70 diastereomeric ratio. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 1H, minor isomer), 7.66 (d, *J* = 8.0 Hz, 1H, major isomer), 7.54 (d, *J* = 7.9 Hz, 1H, major isomer), 7.46 (d, *J* = 7.9 Hz, 1H, minor isomer), 7.30-6.75 (m, 15H major isomer and 16 H minor isomer), 6.44 (s, 1H, major isomer), 5.17-5.13 (m, 1H, major and minor isomer), 4.80-4.76 (m, 1H, major and minor isomer), 4.02 (dd, *J* = 5.5, 2.7 Hz, 1H, major isomer), 3.99 (t, *J* = 5.8 Hz, 1H, minor isomer), 3.81 (s, 3H, major isomer), 3.76 (s, 3H, minor isomer), 3.71 (s, 3H, minor isomer), 3.64 (s, 3H, major isomer), 2.41-2.36 (m, 1H, minor isomer), 2.34-2.30 (m, 1H, major isomer), 2.27-2.21 (m, 1H, minor isomer), 2.14 (s, 3H, major isomer), 2.11-2.05 (m, 1H, major isomer), 2.03 (s, 3H, minor isomer), 2.00-1.95 (m, 1H, minor isomer), 1.94-1.89 (m, 1H, major isomer), 1.81-1.76 (m, 1H, minor isomer), 1.68-1.64 (m, 1H, major isomer) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major and minor isomer): δ = 158.1, 158.1, 138.4, 138.3, 137.9, 137.8, 137.4, 137.4, 136.5, 136.4, 136.2, 136.0, 129.1, 128.8, 128.6, 128.6, 128.5, 128.3, 127.8, 127.7, 127.1, 126.9, 126.5, 126.4, 126.3, 126.3, 126.1, 126.0, 125.9, 123.3, 122.5, 121.3, 121.1, 120.8, 120.8, 120.7, 119.6, 119.3, 118.6,

118.5, 118.1, 118.0, 113.8, 113.8, 109.3, 109.3, 109.2, 109.2, 55.2, 55.2, 46.5, 46.3, 37.9, 36.7, 36.5, 36.4, 34.5, 32.6, 32.6, 31.1, 30.1, 29.7, 29.2, 28.2 ppm (one carbon is missing due to overlapping); IR (neat, ν/cm^{-1}): 3046, 2926, 2858, 1603, 1509, 1462, 1453, 1374, 1327, 1244, 1176, 1031, 908, 832, 806, 734, 699, 561; HRMS (ESI): m/z: calcd for $C_{36}H_{34}N_2NaO^+$: 533.2563, found: 533.2563.

6. X-ray of structure (16h)

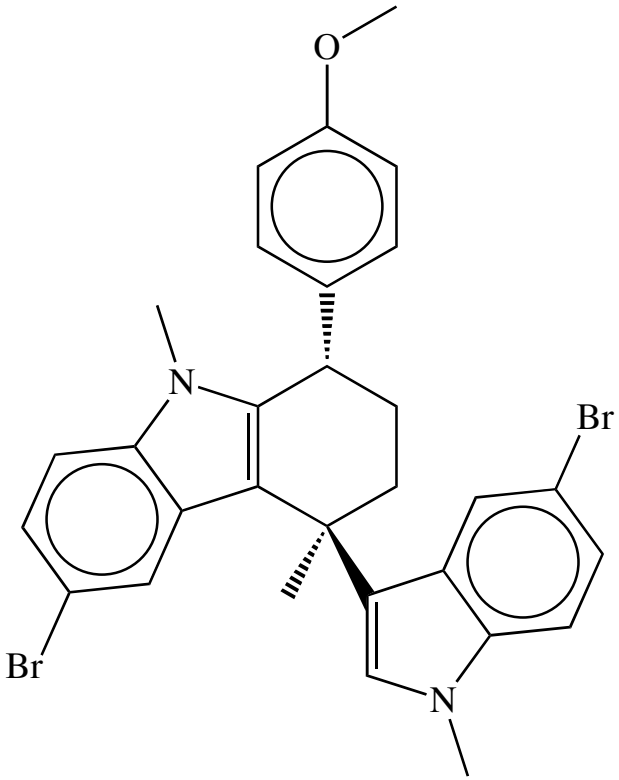


Figure Captions

1. *ORTEP*[1] representation of the molecule (50% probability ellipsoids; H-atoms given

   arbitrary displacement parameters for clarity)

Definition of Terms

Function minimized: S$w(F_o^2 - F_c^2)^2$

where $w = [s^2(F_o^2) + (aP)^2 + bP]^{-1}$ and $P = (F_o^2 + 2F_c^2)/3$

$F_o^2 = S(C - RB)/Lp$

and $s^2(F_o^2) = S^2(C + R^2B)/Lp^2$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan time to background counting time

B = Total background count

Lp = Lorentz-polarization factor

R-factors: $R_{int} = S|\langle F_o^2\rangle - F_o^2|/SF_o^2$ summed only over reflections for which more than one symmetry equivalent was measured.

$R(F) = S||F_o| - |F_c||/S|F_o|$ summed over all observed reflections.

$wR(F^2) = [Sw(F_o^2 - F_c^2)^2/Sw(F_o^2)^2]^{1/2}$ summed over all reflections.

Standard deviation of an observation of unit weight (goodness of fit):

$[Sw(F_o^2 - F_c^2)^2/(N_o - N_v)]^{1/2}$

where N_o = number of observations; N_v = number of variables

NOTES

The structure of $C_{30}H_{28}Br_2N_2O$ (GA12-GO-30-2-F4) has been solved and refined successfully. The structure is not quite that which was expected. The five-membered ring fused to the central six-membered ring is connected the other way around. Since the space group is centrosymmetric, the compound in the crystal is racemic. There are two molecules in the asymmetric unit and these have the same configuration and almost identical conformations. The r.m.s. fit of the non-hydrogen atoms of the two molecules is 0.13 Å.

EXPERIMENTAL

Crystal-Structure Determination. – A crystal of $C_{30}H_{28}Br_2N_2O$, obtained from diethyl ether, was mounted on a glass fibre and used for a low-temperature X-ray structure determination. All measurements were made on an *Agilent Technologies SuperNova* area-detector diffractometer[2] using Mo *K*a radiation (l = 0.71073 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler. The unit cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of 20471 reflections in the range $4° < 2q < 61°$. A total of 728 frames were collected using w scans with k offsets, 35.0 seconds exposure time and a rotation angle of 1.0° per frame, and a crystal-detector distance of 55.0 mm.

Data reduction was performed with *CrysAlisPro*[2]. The intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction using spherical harmonics[2] was applied. The space group was determined from packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure. Equivalent reflections were merged. The data collection and refinement parameters are given in *Table 1*. A view of the molecule is shown in the *Figure*.

The structure was solved by direct methods using *SHELXS97* [3], which revealed the positions of all non-hydrogen atoms. There are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program *PLATON*[8], but none could be found. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were placed in

geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom ($1.5U_{eq}$ for the methyl groups). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimised the function $Sw(F_o^2 - F_c^2)^2$. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. Plots of $Sw(F_o^2-F_c^2)^2$ versus $F_c/F_c(\max)$ and resolution showed no unusual trends. A correction for secondary extinction was not applied.

Neutral atom scattering factors for non-hydrogen atoms were taken from Maslen, Fox and O'Keefe[4a], and the scattering factors for H-atoms were taken from Stewart, Davidson and Simpson[5]. Anomalous dispersion effects were included in F_c[6]; the values for f' and f'' were those of Creagh and McAuley[4b]. The values of the mass attenuation coefficients are those of Creagh and Hubbel[4c]. The *SHELXL97* program[7] was used for all calculations.

REFERENCES

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(2) *CrysAlisPro*, Version 1.171.34.49, Agilent Technologies, Yarnton, Oxfordshire, England, 2011.

(3) G.M. Sheldrick, *Acta Crystallogr. Sect. A*, **2008**, *64*, 112-122.

(4) a) E.N. Maslen, A.G. Fox, M.A. O'Keefe, in 'International Tables for Crystallography', Ed. A.J.C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, pp. 477-486; b) D.C. Creagh, W.J. McAuley, *ibid*. Table 4.2.6.8, pp. 219-222; c) D.C. Creagh, J.H. Hubbell, *ibid*. Table 4.2.4.3, pp. 200-206.

(5) R.F. Stewart, E.R. Davidson, W.T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175-3187.

(6) J.A. Ibers, W.C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781-782.

(7) G.M. Sheldrick, *Acta Crystallogr. Sect. A*, **2008**, *64*, 112-122.

(8) A.L. Spek, *PLATON*, *Program for the Analysis of Molecular Geometry*, University of Utrecht, The Netherlands, 2011.

Table 1. *Crystallographic Data*

Crystallised from		diethyl ether
Empirical formula		$C_{30}H_{28}Br_2N_2O$
Formula weight [g mol^{-1}]		592.37
Crystal colour, habit		colourless, tablet
Crystal dimensions [mm]		0.10 □ 0.25 □ 0.28
Temperature [K]		160(1)
Crystal system		triclinic
Space group		$P\bar{1}$ (#2)
Z		4
Reflections for cell determination		20471
2q range for cell determination [°]		4−61
Unit cell parameters	a [Å]	9.7972(2)
	b [Å]	13.3959(3)
	c [Å]	19.9928(4)
	a [°]	74.5823(19)
	b [°]	88.9965(17)
	g [°]	89.8679(18)
	V [Å^3]	2529.09(9)
F(000)		1200
D_x [g cm^{-3}]		1.556
m(Mo Ka) [mm^{-1}]		3.241
Scan type		w

$2q_{(max)}$ [°]	61.0
Transmission factors (min; max)	0.663; 1.000
Total reflections measured	50270
Symmetry independent reflections	13851
R_{int}	0.033
Reflections with $I > 2s(I)$	11178
Reflections used in refinement	13851
Parameters refined	639
Final $R(F)$ [$I > 2s(I)$ reflections]	0.0555
$wR(F^2)$ (all data)	0.1358
Weights:	$w = [s^2(F_o^2) + (0.0360P)^2 + 9.0208P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.106
Final D_{max}/s	0.001
Dr (max; min) [e Å^{-3}]	1.88; -1.19
$s(d_{(C-C)})$ [Å]	0.00 – 0.00

TABLE 2. Bond lengths (Å) with standard uncertainties in parentheses.

Br(1) -C(9)	1.915(4)	Br(3) -C(39)	1.913(4)
Br(2) -C(19)	1.910(4)	Br(4) -C(49)	1.908(4)
O(1) -C(27)	1.368(4)	O(2) -C(57)	1.366(5)
O(1) -C(30)	1.424(6)	O(2) -C(60)	1.421(5)
N(1) -C(12)	1.376(5)	N(3) -C(42)	1.381(5)
N(1) -C(1)	1.390(5)	N(3) -C(31)	1.387(4)
N(1) -C(13)	1.449(5)	N(3) -C(43)	1.451(5)
N(2) -C(22)	1.368(5)	N(4) -C(52)	1.374(5)
N(2) -C(15)	1.379(5)	N(4) -C(45)	1.382(5)
N(2) -C(23)	1.453(5)	N(4) -C(53)	1.455(5)
C(1) -C(2)	1.359(5)	C(31) -C(32)	1.373(5)
C(1) -C(6)	1.496(5)	C(31) -C(36)	1.498(5)
C(2) -C(7)	1.443(5)	C(32) -C(37)	1.443(5)
C(2) -C(3)	1.521(5)	C(32) -C(33)	1.519(5)
C(3) -C(16)	1.522(5)	C(33) -C(46)	1.517(5)
C(3) -C(14)	1.541(5)	C(33) -C(44)	1.534(5)
C(3) -C(4)	1.554(5)	C(33) -C(34)	1.543(5)
C(4) -C(5)	1.514(6)	C(34) -C(35)	1.524(6)
C(5) -C(6)	1.545(5)	C(35) -C(36)	1.544(6)
C(6) -C(24)	1.517(5)	C(36) -C(54)	1.522(5)
C(7) -C(8)	1.405(5)	C(37) -C(38)	1.404(5)
C(7) -C(12)	1.419(5)	C(37) -C(42)	1.414(5)
C(8) -C(9)	1.388(5)	C(38) -C(39)	1.384(5)
C(9) -C(10)	1.403(5)	C(39) -C(40)	1.374(6)

C(10) -C(11)	1.372(5)	C(40) -C(41)	1.396(6)
C(11) -C(12)	1.391(5)	C(41) -C(42)	1.391(5)
C(15) -C(16)	1.363(5)	C(45) -C(46)	1.365(5)
C(16) -C(17)	1.448(5)	C(46) -C(47)	1.445(5)
C(17) -C(22)	1.411(5)	C(47) -C(48)	1.407(5)
C(17) -C(18)	1.413(5)	C(47) -C(52)	1.418(5)
C(18) -C(19)	1.378(5)	C(48) -C(49)	1.374(5)
C(19) -C(20)	1.393(6)	C(49) -C(50)	1.397(6)
C(20) -C(21)	1.379(6)	C(50) -C(51)	1.371(6)
C(21) -C(22)	1.402(5)	C(51) -C(52)	1.392(5)
C(24) -C(25)	1.395(5)	C(54) -C(55)	1.388(5)
C(24) -C(29)	1.399(5)	C(54) -C(59)	1.395(5)
C(25) -C(26)	1.384(5)	C(55) -C(56)	1.393(5)
C(26) -C(27)	1.393(5)	C(56) -C(57)	1.389(5)
C(27) -C(28)	1.393(5)	C(57) -C(58)	1.399(5)
C(28) -C(29)	1.381(5)	C(58) -C(59)	1.379(5)

TABLE 3. Bond angles (°) with standard uncertainties in parentheses.

C(27) -O(1) -C(30)	116.4(3)	C(57) -O(2) -C(60)	115.9(3)
C(12) -N(1) -C(1)	108.1(3)	C(42) -N(3) -C(31)	107.7(3)
C(12) -N(1) -C(13)	124.2(3)	C(42) -N(3) -C(43)	124.8(3)
C(1) -N(1) -C(13)	127.5(3)	C(31) -N(3) -C(43)	127.3(3)
C(22) -N(2) -C(15)	108.2(3)	C(52) -N(4) -C(45)	108.5(3)
C(22) -N(2) -C(23)	125.5(3)	C(52) -N(4) -C(53)	125.1(3)
C(15) -N(2) -C(23)	126.4(3)	C(45) -N(4) -C(53)	126.4(3)
C(2) -C(1) -N(1)	110.6(3)	C(32) -C(31) -N(3)	110.8(3)
C(2) -C(1) -C(6)	127.8(3)	C(32) -C(31) -C(36)	126.8(3)
N(1) -C(1) -C(6)	121.6(3)	N(3) -C(31) -C(36)	122.4(3)
C(1) -C(2) -C(7)	106.6(3)	C(31) -C(32) -C(37)	106.2(3)
C(1) -C(2) -C(3)	123.4(3)	C(31) -C(32) -C(33)	123.8(3)
C(7) -C(2) -C(3)	129.8(3)	C(37) -C(32) -C(33)	129.9(3)
C(2) -C(3) -C(16)	111.5(3)	C(46) -C(33) -C(32)	111.4(3)
C(2) -C(3) -C(14)	109.9(3)	C(46) -C(33) -C(44)	110.8(3)
C(16) -C(3) -C(14)	110.8(3)	C(32) -C(33) -C(44)	110.5(3)
C(2) -C(3) -C(4)	106.9(3)	C(46) -C(33) -C(34)	109.9(3)
C(16) -C(3) -C(4)	109.8(3)	C(32) -C(33) -C(34)	106.3(3)
C(14) -C(3) -C(4)	107.7(3)	C(44) -C(33) -C(34)	107.8(3)
C(5) -C(4) -C(3)	113.2(3)	C(35) -C(34) -C(33)	112.7(3)
C(4) -C(5) -C(6)	111.8(3)	C(34) -C(35) -C(36)	112.1(3)
C(1) -C(6) -C(24)	113.6(3)	C(31) -C(36) -C(54)	113.0(3)

C(1) -C(6) -C(5)	107.3(3)	C(31) -C(36) -C(35)	108.0(3)
C(24) -C(6) -C(5)	111.7(3)	C(54) -C(36) -C(35)	111.9(3)
C(8) -C(7) -C(12)	118.1(3)	C(38) -C(37) -C(42)	118.1(3)
C(8) -C(7) -C(2)	135.1(3)	C(38) -C(37) -C(32)	135.0(3)
C(12) -C(7) -C(2)	106.7(3)	C(42) -C(37) -C(32)	106.8(3)
C(9) -C(8) -C(7)	117.6(3)	C(39) -C(38) -C(37)	117.5(3)
C(8) -C(9) -C(10)	123.7(3)	C(40) -C(39) -C(38)	124.1(3)
C(8) -C(9) -Br(1)	118.3(3)	C(40) -C(39) -Br(3)	118.2(3)
C(10) -C(9) -Br(1)	117.8(3)	C(38) -C(39) -Br(3)	117.6(3)
C(11) -C(10) -C(9)	118.9(3)	C(39) -C(40) -C(41)	119.9(3)
C(10) -C(11) -C(12)	118.7(3)	C(42) -C(41) -C(40)	116.9(3)
N(1) -C(12) -C(11)	129.0(3)	N(3) -C(42) -C(41)	127.9(3)
N(1) -C(12) -C(7)	108.1(3)	N(3) -C(42) -C(37)	108.5(3)
C(11) -C(12) -C(7)	122.9(3)	C(41) -C(42) -C(37)	123.6(3)
C(16) -C(15) -N(2)	111.1(3)	C(46) -C(45) -N(4)	111.0(3)
C(15) -C(16) -C(17)	105.7(3)	C(45) -C(46) -C(47)	105.6(3)
C(15) -C(16) -C(3)	126.8(3)	C(45) -C(46) -C(33)	127.3(3)
C(17) -C(16) -C(3)	127.5(3)	C(47) -C(46) -C(33)	127.1(3)
C(22) -C(17) -C(18)	118.1(3)	C(48) -C(47) -C(52)	117.7(3)
C(22) -C(17) -C(16)	106.8(3)	C(48) -C(47) -C(46)	134.8(3)
C(18) -C(17) -C(16)	135.1(3)	C(52) -C(47) -C(46)	107.4(3)
C(19) -C(18) -C(17)	118.1(4)	C(49) -C(48) -C(47)	118.3(3)
C(18) -C(19) -C(20)	123.4(4)	C(48) -C(49) -C(50)	123.3(3)
C(18) -C(19) -Br(2)	118.3(3)	C(48) -C(49) -Br(4)	118.5(3)

C(20) -C(19) -Br(2)	118.3(3)	C(50) -C(49) -Br(4)	118.2(3)
C(21) -C(20) -C(19)	119.6(4)	C(51) -C(50) -C(49)	119.5(3)
C(20) -C(21) -C(22)	118.1(4)	C(50) -C(51) -C(52)	118.3(3)
N(2) -C(22) -C(21)	129.1(4)	N(4) -C(52) -C(51)	129.7(3)
N(2) -C(22) -C(17)	108.3(3)	N(4) -C(52) -C(47)	107.4(3)
C(21) -C(22) -C(17)	122.6(4)	C(51) -C(52) -C(47)	122.8(3)
C(25) -C(24) -C(29)	117.4(3)	C(55) -C(54) -C(59)	118.0(3)
C(25) -C(24) -C(6)	119.2(3)	C(55) -C(54) -C(36)	119.1(3)
C(29) -C(24) -C(6)	123.4(3)	C(59) -C(54) -C(36)	122.9(3)
C(26) -C(25) -C(24)	122.4(3)	C(54) -C(55) -C(56)	122.0(3)
C(25) -C(26) -C(27)	119.0(3)	C(57) -C(56) -C(55)	119.0(3)
O(1) -C(27) -C(26)	124.2(3)	O(2) -C(57) -C(56)	124.5(3)
O(1) -C(27) -C(28)	116.0(3)	O(2) -C(57) -C(58)	115.7(3)
C(26) -C(27) -C(28)	119.8(3)	C(56) -C(57) -C(58)	119.8(3)
C(29) -C(28) -C(27)	120.2(3)	C(59) -C(58) -C(57)	120.2(3)
C(28) -C(29) -C(24)	121.1(3)	C(58) -C(59) -C(54)	121.1(3)

TABLE 4. Torsion angles (°) with standard uncertainties in parentheses.

C(12)	-N(1)	-C(1)	-C(2)	-1.0(4)	C(42)	-N(3)	-C(31)	-C(32)	-0.7(4)
C(13)	-N(1)	-C(1)	-C(2)	-175.4(4)	C(43)	-N(3)	-C(31)	-C(32)	-174.9(4)
C(12)	-N(1)	-C(1)	-C(6)	178.4(3)	C(42)	-N(3)	-C(31)	-C(36)	177.3(3)
C(13)	-N(1)	-C(1)	-C(6)	4.1(6)	C(43)	-N(3)	-C(31)	-C(36)	3.1(6)
N(1)	-C(1)	-C(2)	-C(7)	0.5(4)	N(3)	-C(31)	-C(32)	-C(37)	0.4(4)
C(6)	-C(1)	-C(2)	-C(7)	-178.9(3)	C(36)	-C(31)	-C(32)	-C(37)	-177.5(3)
N(1)	-C(1)	-C(2)	-C(3)	175.8(3)	N(3)	-C(31)	-C(32)	-C(33)	176.4(3)
C(6)	-C(1)	-C(2)	-C(3)	-3.6(6)	C(36)	-C(31)	-C(32)	-C(33)	-1.6(6)
C(1)	-C(2)	-C(3)	-C(16)	106.5(4)	C(31)	-C(32)	-C(33)	-C(46)	101.4(4)
C(7)	-C(2)	-C(3)	-C(16)	-79.3(4)	C(37)	-C(32)	-C(33)	-C(46)	-83.7(4)
C(1)	-C(2)	-C(3)	-C(14)	-130.2(4)	C(31)	-C(32)	-C(33)	-C(44)	-134.9(4)
C(7)	-C(2)	-C(3)	-C(14)	44.0(5)	C(37)	-C(32)	-C(33)	-C(44)	40.0(5)
C(1)	-C(2)	-C(3)	-C(4)	-13.6(5)	C(31)	-C(32)	-C(33)	-C(34)	-18.2(4)
C(7)	-C(2)	-C(3)	-C(4)	160.7(3)	C(37)	-C(32)	-C(33)	-C(34)	156.6(3)
C(2)	-C(3)	-C(4)	-C(5)	46.7(4)	C(46)	-C(33)	-C(34)	-C(35)	-70.4(4)
C(16)	-C(3)	-C(4)	-C(5)	-74.4(4)	C(32)	-C(33)	-C(34)	-C(35)	50.3(4)
C(14)	-C(3)	-C(4)	-C(5)	164.9(3)	C(44)	-C(33)	-C(34)	-C(35)	168.8(3)
C(3)	-C(4)	-C(5)	-C(6)	-65.8(4)	C(33)	-C(34)	-C(35)	-C(36)	-66.1(4)
C(2)	-C(1)	-C(6)	-C(24)	112.7(4)	C(32)	-C(31)	-C(36)	-C(54)	114.9(4)
N(1)	-C(1)	-C(6)	-C(24)	-66.6(4)	N(3)	-C(31)	-C(36)	-C(54)	-62.8(5)
C(2)	-C(1)	-C(6)	-C(5)	-11.2(5)	C(32)	-C(31)	-C(36)	-C(35)	-9.4(5)
N(1)	-C(1)	-C(6)	-C(5)	169.4(3)	N(3)	-C(31)	-C(36)	-C(35)	172.8(3)
C(4)	-C(5)	-C(6)	-C(1)	43.6(4)	C(34)	-C(35)	-C(36)	-C(31)	41.0(4)
C(4)	-C(5)	-C(6)	-C(24)	-81.6(4)	C(34)	-C(35)	-C(36)	-C(54)	-84.0(4)
C(1)	-C(2)	-C(7)	-C(8)	176.4(4)	C(31)	-C(32)	-C(37)	-C(38)	176.4(4)
C(3)	-C(2)	-C(7)	-C(8)	1.4(6)	C(33)	-C(32)	-C(37)	-C(38)	0.8(7)

C(1) -C(2) -C(7) -C(12)	0.2(4)	C(31) -C(32) -C(37) -C(42)	0.0(4)
C(3) -C(2) -C(7) -C(12)	-174.8(3)	C(33) -C(32) -C(37) -C(42)	-175.6(3)
C(12) -C(7) -C(8) -C(9)	0.9(5)	C(42) -C(37) -C(38) -C(39)	1.6(5)
C(2) -C(7) -C(8) -C(9)	-174.9(4)	C(32) -C(37) -C(38) -C(39)	-174.5(4)
C(7) -C(8) -C(9) -C(10)	-2.7(6)	C(37) -C(38) -C(39) -C(40)	-2.4(6)
C(7) -C(8) -C(9) -Br(1)	173.9(3)	C(37) -C(38) -C(39) -Br(3)	173.2(3)
C(8) -C(9) -C(10) -C(11)	2.4(6)	C(38) -C(39) -C(40) -C(41)	1.1(6)
Br(1) -C(9) -C(10) -C(11)	-174.3(3)	Br(3) -C(39) -C(40) -C(41)	-174.5(3)
C(9) -C(10) -C(11) -C(12)	-0.2(6)	C(39) -C(40) -C(41) -C(42)	1.1(6)
C(1) -N(1) -C(12) -C(11)	-177.7(4)	C(31) -N(3) -C(42) -C(41)	-177.2(4)
C(13) -N(1) -C(12) -C(11)	-3.1(6)	C(43) -N(3) -C(42) -C(41)	-2.9(6)
C(1) -N(1) -C(12) -C(7)	1.1(4)	C(31) -N(3) -C(42) -C(37)	0.7(4)
C(13) -N(1) -C(12) -C(7)	175.7(3)	C(43) -N(3) -C(42) -C(37)	175.1(4)
C(10) -C(11) -C(12) -N(1)	177.1(4)	C(40) -C(41) -C(42) -N(3)	175.8(4)
C(10) -C(11) -C(12) -C(7)	-1.5(6)	C(40) -C(41) -C(42) -C(37)	-1.8(6)
C(8) -C(7) -C(12) -N(1)	-177.7(3)	C(38) -C(37) -C(42) -N(3)	-177.6(3)
C(2) -C(7) -C(12) -N(1)	-0.8(4)	C(32) -C(37) -C(42) -N(3)	-0.5(4)
C(8) -C(7) -C(12) -C(11)	1.2(5)	C(38) -C(37) -C(42) -C(41)	0.5(6)
C(2) -C(7) -C(12) -C(11)	178.1(3)	C(32) -C(37) -C(42) -C(41)	177.6(4)
C(22) -N(2) -C(15) -C(16)	-1.2(4)	C(52) -N(4) -C(45) -C(46)	-0.4(4)
C(23) -N(2) -C(15) -C(16)	180.0(4)	C(53) -N(4) -C(45) -C(46)	-179.0(4)
N(2) -C(15) -C(16) -C(17)	0.3(4)	N(4) -C(45) -C(46) -C(47)	-0.3(4)
N(2) -C(15) -C(16) -C(3)	-179.2(3)	N(4) -C(45) -C(46) -C(33)	179.3(3)
C(2) -C(3) -C(16) -C(15)	-12.1(5)	C(32) -C(33) -C(46) -C(45)	-5.0(5)
C(14) -C(3) -C(16) -C(15)	-134.9(4)	C(44) -C(33) -C(46) -C(45)	-128.5(4)
C(4) -C(3) -C(16) -C(15)	106.2(4)	C(34) -C(33) -C(46) -C(45)	112.5(4)
C(2) -C(3) -C(16) -C(17)	168.5(3)	C(32) -C(33) -C(46) -C(47)	174.5(3)
C(14) -C(3) -C(16) -C(17)	45.7(5)	C(44) -C(33) -C(46) -C(47)	51.0(4)

C(4) -C(3) -C(16) -C(17)	-73.2(4)	C(34) -C(33) -C(46) -C(47)	-68.0(4)
C(15) -C(16) -C(17) -C(22)	0.6(4)	C(45) -C(46) -C(47) -C(48)	-179.9(4)
C(3) -C(16) -C(17) -C(22)	-179.9(3)	C(33) -C(46) -C(47) -C(48)	0.5(6)
C(15) -C(16) -C(17) -C(18)	-179.7(4)	C(45) -C(46) -C(47) -C(52)	0.8(4)
C(3) -C(16) -C(17) -C(18)	-0.1(7)	C(33) -C(46) -C(47) -C(52)	-178.8(3)
C(22) -C(17) -C(18) -C(19)	2.6(5)	C(52) -C(47) -C(48) -C(49)	1.3(5)
C(16) -C(17) -C(18) -C(19)	-177.2(4)	C(46) -C(47) -C(48) -C(49)	-177.9(4)
C(17) -C(18) -C(19) -C(20)	0.8(6)	C(47) -C(48) -C(49) -C(50)	0.9(6)
C(17) -C(18) -C(19) -Br(2)	-179.5(3)	C(47) -C(48) -C(49) -Br(4)	-178.6(3)
C(18) -C(19) -C(20) -C(21)	-2.9(6)	C(48) -C(49) -C(50) -C(51)	-2.0(6)
Br(2) -C(19) -C(20) -C(21)	177.4(3)	Br(4) -C(49) -C(50) -C(51)	177.5(3)
C(19) -C(20) -C(21) -C(22)	1.6(6)	C(49) -C(50) -C(51) -C(52)	0.7(6)
C(15) -N(2) -C(22) -C(21)	-175.4(4)	C(45) -N(4) -C(52) -C(51)	-176.9(4)
C(23) -N(2) -C(22) -C(21)	3.4(6)	C(53) -N(4) -C(52) -C(51)	1.8(6)
C(15) -N(2) -C(22) -C(17)	1.5(4)	C(45) -N(4) -C(52) -C(47)	0.9(4)
C(23) -N(2) -C(22) -C(17)	-179.6(4)	C(53) -N(4) -C(52) -C(47)	179.6(4)
C(20) -C(21) -C(22) -N(2)	178.3(4)	C(50) -C(51) -C(52) -N(4)	178.9(4)
C(20) -C(21) -C(22) -C(17)	1.8(6)	C(50) -C(51) -C(52) -C(47)	1.5(5)
C(18) -C(17) -C(22) -N(2)	178.9(3)	C(48) -C(47) -C(52) -N(4)	179.5(3)
C(16) -C(17) -C(22) -N(2)	-1.3(4)	C(46) -C(47) -C(52) -N(4)	-1.1(4)
C(18) -C(17) -C(22) -C(21)	-3.9(5)	C(48) -C(47) -C(52) -C(51)	-2.5(5)
C(16) -C(17) -C(22) -C(21)	175.9(3)	C(46) -C(47) -C(52) -C(51)	176.9(3)
C(1) -C(6) -C(24) -C(25)	158.2(3)	C(31) -C(36) -C(54) -C(55)	153.9(3)
C(5) -C(6) -C(24) -C(25)	-80.2(4)	C(35) -C(36) -C(54) -C(55)	-83.9(4)
C(1) -C(6) -C(24) -C(29)	-21.2(5)	C(31) -C(36) -C(54) -C(59)	-27.7(5)
C(5) -C(6) -C(24) -C(29)	100.3(4)	C(35) -C(36) -C(54) -C(59)	94.5(4)
C(29) -C(24) -C(25) -C(26)	-0.7(6)	C(59) -C(54) -C(55) -C(56)	0.9(5)
C(6) -C(24) -C(25) -C(26)	179.8(4)	C(36) -C(54) -C(55) -C(56)	179.4(3)

C(24) -C(25) -C(26) -C(27)	1.3(6)	C(54) -C(55) -C(56) -C(57)	-0.8(6)
C(30) -O(1) -C(27) -C(26)	-0.6(6)	C(60) -O(2) -C(57) -C(56)	0.7(6)
C(30) -O(1) -C(27) -C(28)	-179.8(4)	C(60) -O(2) -C(57) -C(58)	-178.1(4)
C(25) -C(26) -C(27) -O(1)	179.1(4)	C(55) -C(56) -C(57) -O(2)	-179.0(3)
C(25) -C(26) -C(27) -C(28)	-1.8(6)	C(55) -C(56) -C(57) -C(58)	-0.3(5)
O(1) -C(27) -C(28) -C(29)	-179.0(4)	O(2) -C(57) -C(58) -C(59)	-180.0(3)
C(26) -C(27) -C(28) -C(29)	1.8(6)	C(56) -C(57) -C(58) -C(59)	1.2(6)
C(27) -C(28) -C(29) -C(24)	-1.3(6)	C(57) -C(58) -C(59) -C(54)	-1.0(6)
C(25) -C(24) -C(29) -C(28)	0.7(6)	C(55) -C(54) -C(59) -C(58)	0.0(6)
C(6) -C(24) -C(29) -C(28)	-179.8(4)	C(36) -C(54) -C(59) -C(58)	-178.4(4)

7. X-ray of structure (24d)

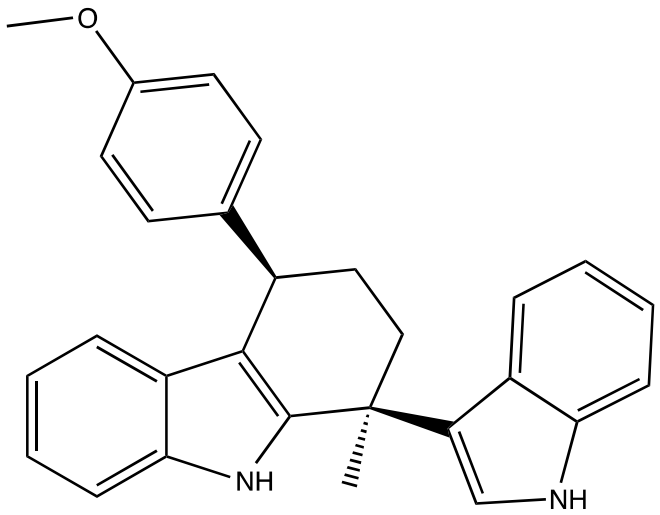

Figure Captions

1. *ORTEP*[1] representation of the molecule (50% probability ellipsoids; H-atoms given arbitrary displacement parameters for clarity)

2. Molecular packing projected down the *a*-axis showing the hydrogen bonding scheme

   (equivalent isotropic spheres for atoms; uninvolved H-atoms omitted for clarity)

Definition of Terms

Function minimized: $\Sigma w(F_o^2 - F_c^2)^2$

where $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$ and $P = (F_o^2 + 2F_c^2)/3$

$F_o^2 = S(C - RB)/Lp$

and $\sigma^2(F_o^2) = S^2(C + R^2B)/Lp^2$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan time to background counting time

B = Total background count

Lp = Lorentz-polarization factor

R-factors: $R_{int} = \Sigma|<F_o^2> - F_o^2|/\Sigma F_o^2$ summed only over reflections for which more than one symmetry equivalent was measured.

$R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ summed over all observed reflections.

$wR(F^2) = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$ summed over all reflections.

Standard deviation of an observation of unit weight (goodness of fit):

$[\Sigma w(F_o^2 - F_c^2)^2/(N_o - N_v)]^{1/2}$

where N_o = number of observations; N_v = number of variables

NOTES

The structure of $C_{28}H_{26}N_2O$ (GQ-20-1-F30) has been solved and refined successfully with no unusual features. Since the space group is centrosymmetric, the compound in the crystal is racemic. The relative configuration of the two stereogenic centres is 3*S**,6*R** (using the atom numbering in the X-ray model).

EXPERIMENTAL

Crystal-Structure Determination. – A crystal of $C_{28}H_{26}N_2O$, obtained from CH_2Cl_2, was mounted on a glass fibre and used for a low-temperature X-ray structure determination. All measurements were made on an *Agilent Technologies SuperNova* area-detector diffractometer[2] using Cu $K\alpha$ radiation (λ = 1.54184 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler. The unit cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of 8821 reflections in the range 4° < 2θ < 153°. A total of 1878 frames were collected using ω scans with κ offsets, 2.3-9.2 seconds exposure time and a rotation angle of 1.0° per frame, and a crystal-detector distance of 55.0 mm.

Data reduction was performed with *CrysAlisPro*[2]. The intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction using spherical harmonics[2] was applied. The space group was uniquely determined by the systematic absences. Equivalent reflections were merged. The data collection and refinement parameters are given in *Table 1*. A view of the molecule is shown in the *Figure*.

The structure was solved by direct methods using *SHELXS97*[3], which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent atom (1.5U_{eq} for the methyl groups). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_O^2 - F_C^2)^2$. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. Plots of $\Sigma w(F_O^2 - F_C^2)^2$ versus F_C/F_C(max) and resolution showed no unusual trends. A correction for secondary extinction was not applied.

Neutral atom scattering factors for non-hydrogen atoms were taken from Maslen, Fox and O'Keefe[4a], and the scattering factors for H-atoms were taken from Stewart, Davidson and Simpson[5]. Anomalous dispersion effects were included in F_c[6]; the values for *f'* and *f''* were those of Creagh and McAuley[4b]. The values of the mass attenuation coefficients are those of Creagh and Hubbel[4c]. The *SHELXL97* program[7] was used for all calculations.

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Table 1. *Crystallographic Data*

Crystallised from		CH_2Cl_2
Empirical formula		$C_{28}H_{26}N_2O$
Formula weight [g mol^{-1}]		406.53
Crystal colour, habit		colourless, plate
Crystal dimensions [mm]		0.04 × 0.05 × 0.30
Temperature [K]		160(1)
Crystal system		monoclinic
Space group		$P2_1/n$ (#14)
Z		4
Reflections for cell determination		8821
2θ range for cell determination [°]		4–153
Unit cell parameters	a [Å]	10.87950(13)
	b [Å]	10.63345(11)
	c [Å]	19.0796(3)
	α [°]	90
	β [°]	95.3655(13)
	γ [°]	90
	V [Å^3]	2197.58(5)
F(000)		864
D_x [g cm^{-3}]		1.229
μ(Cu $K\alpha$) [mm^{-1}]		0.580
Scan type		ω

$2\theta_{(max)}$ [°]	153.2
Transmission factors (min; max)	0.096; 1.000
Total reflections measured	22996
Symmetry independent reflections	4582
R_{int}	0.060
Reflections with $I > 2\sigma(I)$	3750
Reflections used in refinement	4582
Parameters refined	282
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0608
$wR(F^2)$ (all data)	0.1717
Weights:	$w = [\sigma^2(F_o^2) + (0.0900P)^2 + 0.9378P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.056
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.62; -0.34
$\sigma(d_{(C-C)})$ [Å]	0.002 – 0.004

TABLE 2. Bond lengths (Å) with standard uncertainties in parentheses.

O(1)	-C(25)	1.371(2)	C(8)	-C(9)	1.381(3)
O(1)	-C(28)	1.426(2)	C(9)	-C(10)	1.402(3)
N(1)	-C(12)	1.372(2)	C(10)	-C(11)	1.378(3)
N(1)	-C(2)	1.375(2)	C(11)	-C(12)	1.396(2)
N(2)	-C(21)	1.365(3)	C(14)	-C(15)	1.357(3)
N(2)	-C(14)	1.370(3)	C(15)	-C(16)	1.446(3)
C(1)	-C(2)	1.369(2)	C(16)	-C(17)	1.400(3)
C(1)	-C(7)	1.436(2)	C(16)	-C(21)	1.406(3)
C(1)	-C(6)	1.502(2)	C(17)	-C(18)	1.388(3)
C(2)	-C(3)	1.499(2)	C(18)	-C(19)	1.410(3)
C(3)	-C(15)	1.520(3)	C(19)	-C(20)	1.356(4)
C(3)	-C(13)	1.547(3)	C(20)	-C(21)	1.393(3)
C(3)	-C(4)	1.554(3)	C(22)	-C(27)	1.386(2)
C(4)	-C(5)	1.525(3)	C(22)	-C(23)	1.393(2)
C(5)	-C(6)	1.544(3)	C(23)	-C(24)	1.378(3)
C(6)	-C(22)	1.518(2)	C(24)	-C(25)	1.390(2)
C(7)	-C(8)	1.409(3)	C(25)	-C(26)	1.385(2)
C(7)	-C(12)	1.415(2)	C(26)	-C(27)	1.392(2)

TABLE 3. Bond angles (°) with standard uncertainties in parentheses.

C(25)	-O(1)	-C(28)	117.82(14)	N(1)	-C(12) -C(11) 129.27(16)
C(12)	-N(1)	-C(2)	108.78(14)	N(1)	-C(12) -C(7) 107.99(14)
C(21)	-N(2)	-C(14)	109.2(2)	C(11)	-C(12) -C(7) 122.73(16)
C(2)	-C(1)	-C(7)	106.86(15)	C(15)	-C(14) -N(2) 110.9(2)
C(2)	-C(1)	-C(6)	123.78(17)	C(14)	-C(15) -C(16) 105.16(19)
C(7)	-C(1)	-C(6)	129.16(16)	C(14)	-C(15) -C(3) 125.7(2)
C(1)	-C(2)	-N(1)	109.92(15)	C(16)	-C(15) -C(3) 128.96(18)
C(1)	-C(2)	-C(3)	127.41(16)	C(17)	-C(16) -C(21) 117.45(19)
N(1)	-C(2)	-C(3)	122.55(15)	C(17)	-C(16) -C(15) 134.80(18)
C(2)	-C(3)	-C(15)	111.30(14)	C(21)	-C(16) -C(15) 107.73(19)
C(2)	-C(3)	-C(13)	107.98(15)	C(18)	-C(17) -C(16) 119.8(2)
C(15)	-C(3)	-C(13)	110.09(17)	C(17)	-C(18) -C(19) 120.3(2)
C(2)	-C(3)	-C(4)	106.36(15)	C(20)	-C(19) -C(18) 121.3(2)

C(15) -C(3) -C(4) 110.44(16) C(19) -C(20) -C(21) 117.8(2)

C(13) -C(3) -C(4) 110.58(15) N(2) -C(21) -C(20) 129.8(2)

C(5) -C(4) -C(3) 112.75(16) N(2) -C(21) -C(16) 107.0(2)

C(4) -C(5) -C(6) 112.36(15) C(20) -C(21) -C(16) 123.3(2)

C(1) -C(6) -C(22) 115.01(14) C(27) -C(22) -C(23) 117.14(16)

C(1) -C(6) -C(5) 108.57(15) C(27) -C(22) -C(6) 124.21(15)

C(22) -C(6) -C(5) 111.14(15) C(23) -C(22) -C(6) 118.61(15)

C(8) -C(7) -C(12) 118.18(17) C(24) -C(23) -C(22) 121.73(15)

C(8) -C(7) -C(1) 135.39(17) C(23) -C(24) -C(25) 120.08(15)

C(12) -C(7) -C(1) 106.43(15) O(1) -C(25) -C(26) 124.54(15)

C(9) -C(8) -C(7) 118.88(18) O(1) -C(25) -C(24) 115.86(15)

C(8) -C(9) -C(10) 121.76(18) C(26) -C(25) -C(24) 119.60(16)

C(11) -C(10) -C(9) 120.87(19) C(25) -C(26) -C(27) 119.22(15)

C(10) -C(11) -C(12) 117.58(18) C(22) -C(27) -C(26) 122.23(15)

TABLE 4. Torsion angles (°) with standard uncertainties in parentheses.

C(7)	-C(1)	-C(2)	-N(1)	1.3(2)	N(2)	-C(14)	-C(15) -C(3) 177.5(2)
C(6)	-C(1)	-C(2)	-N(1)	-174.0(1)	C(2)	-C(3)	-C(15) -C(14) 152.0(2)
C(7)	-C(1)	-C(2)	-C(3)	177.2(2)	C(13)	-C(3)	-C(15) -C(14) 32.3(3)
C(6)	-C(1)	-C(2)	-C(3)	1.9(3)	C(4)	-C(3)	-C(15) -C(14) -90.1(3)
C(12)	-N(1)	-C(2)	-C(1)	-1.6(2)	C(2)	-C(3)	-C(15) -C(16) -33.4(3)
C(12)	-N(1)	-C(2)	-C(3)	-177.8(1)	C(13)	-C(3)	-C(15) -C(16) -153.1(2)
C(1)	-C(2)	-C(3)	-C(15)	134.2(2)	C(4)	-C(3)	-C(15) -C(16) 84.5(2)
N(1)	-C(2)	-C(3)	-C(15)	-50.4(2)	C(14)	-C(15)	-C(16) -C(17) 179.8(2)
C(1)	-C(2)	-C(3)	-C(13)	-104.9(2)	C(3)	-C(15)	-C(16) -C(17) 4.3(4)
N(1)	-C(2)	-C(3)	-C(13)	70.6(2)	C(14)	-C(15)	-C(16) -C(21) -1.5(3)
C(1)	-C(2)	-C(3)	-C(4)	13.8(2)	C(3)	-C(15)	-C(16) -C(21) -177.0(2)
N(1)	-C(2)	-C(3)	-C(4)	-170.7(2)	C(21)	-C(16)	-C(17) -C(18) 0.1(3)
C(2)	-C(3)	-C(4)	-C(5)	-45.2(2)	C(15)	-C(16)	-C(17) -C(18) 178.7(2)
C(15)	-C(3)	-C(4)	-C(5)	-166.1(2)	C(16)	-C(17)	-C(18) -C(19) -0.3(3)
C(13)	-C(3)	-C(4)	-C(5)	71.8(2)	C(17)	-C(18)	-C(19) -C(20) 0.2(4)

C(3) -C(4) -C(5) -C(6) 64.7(2) C(18) -C(19) -C(20) -C(21) 0.1(4)

C(2) -C(1) -C(6) -C(22) -112.2(2) C(14) -N(2) -C(21) -C(20) 179.8(3)

C(7) -C(1) -C(6) -C(22) 73.6(2) C(14) -N(2) -C(21) -C(16) 0.5(3)

C(2) -C(1) -C(6) -C(5) 13.0(2) C(19) -C(20) -C(21) -N(2) -179.6(3)

C(7) -C(1) -C(6) -C(5) -161.2(2) C(19) -C(20) -C(21) -C(16) -0.3(4)

C(4) -C(5) -C(6) -C(1) -44.4(2) C(17) -C(16) -C(21) -N(2) 179.6(2)

C(4) -C(5) -C(6) -C(22) 83.1(2) C(15) -C(16) -C(21) -N(2) 0.7(3)

C(2) -C(1) -C(7) -C(8) 179.9(2) C(17) -C(16) -C(21) -C(20) 0.2(3)

C(6) -C(1) -C(7) -C(8) -5.1(3) C(15) -C(16) -C(21) -C(20) -178.7(2)

C(2) -C(1) -C(7) -C(12) -0.5(2) C(1) -C(6) -C(22) -C(27) 24.9(3)

C(6) -C(1) -C(7) -C(12) 174.5(2) C(5) -C(6) -C(22) -C(27) -99.0(2)

C(12) -C(7) -C(8) -C(9) -0.1(2) C(1) -C(6) -C(22) -C(23) -157.3(2)

C(1) -C(7) -C(8) -C(9) 179.5(2) C(5) -C(6) -C(22) -C(23) 78.8(2)

C(7) -C(8) -C(9) -C(10) -0.3(3) C(27) -C(22) -C(23) -C(24) 0.5(3)

C(8) -C(9) -C(10) -C(11) 0.4(3) C(6) -C(22) -C(23) -C(24) -177.4(2)

C(9) -C(10) -C(11) -C(12) -0.0(3) C(22) -C(23) -C(24) -C(25) -0.2(3)

C(2) -N(1) -C(12) -C(11) 179.9(2) C(28) -O(1) -C(25) -C(26) 8.8(3)

C(2) -N(1) -C(12) -C(7) 1.2(2) C(28) -O(1) -C(25) -C(24) -171.8(2)

C(10) -C(11) -C(12) -N(1) -178.9(2) C(23) -C(24) -C(25) -O(1) -179.6(2)

C(10) -C(11) -C(12) -C(7) -0.4(3) C(23) -C(24) -C(25) -C(26) -0.1(3)

C(8) -C(7) -C(12) -N(1) 179.2(1) O(1) -C(25) -C(26) -C(27) 179.4(2)

C(1) -C(7) -C(12) -N(1) -0.5(2) C(24) -C(25) -C(26) -C(27) 0.0(3)

C(8) -C(7) -C(12) -C(11) 0.5(2) C(23) -C(22) -C(27) -C(26) -0.7(3)

C(1) -C(7) -C(12) -C(11) -179.2(2) C(6) -C(22) -C(27) -C(26) 177.1(2)

C(21) -N(2) -C(14) -C(15) -1.5(4) C(25) -C(26) -C(27) -C(22) 0.4(3)

N(2) -C(14) -C(15) -C(16) 1.9(3)

TABLE 5. Selected bond lengths (Å) and angles (°) involving H-atoms.

N(1)	-H(1)	0.880		N(2)	-H(2)	0.880	
C(12)	-N(1)	-H(1)	125.6	C(21)	-N(2)	-H(2)	125.4
C(2)	-N(1)	-H(1)	125.6	C(14)	-N(2)	-H(2)	125.4

TABLE 6. Hydrogen bonding geometry (Å, °).

D	H	A	D-H	H···A	D···A	D-H···A
N(1)-H(1)···O(1')			0.88	2.07	2.8810(19)	153.0

Primed atoms refer to the molecule in the following symmetry related positions:

' *x*, -1+*y*, *z*

Only one of the two N-H groups in the molecule acts as a donor for hydrogen bonds. This intermolecular interaction with the methoxy O-atom of a neighbouring molecule links the molecules into extended chains which run parallel to the [010] direction and can be described by a graph set motif[8] of C(10).

Chapter 6

Conclusions and Outlook

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The role of gold as an important tool in all fields of synthetic organic chemistry is one of the fast growing sectors of modern organic chemistry. In the last twenty years, gold has been recognized as a powerful carbophilic Lewis acid able to activate unsaturated moieties triggering the discovery of new and original methods to form new C-C bonds. In this context, a rapidly developing area involves the rearangement of propargyl esters towards 1,2-acyloxy migration and/or [3,3]-sigmatropic rearrangement to construct molecular complexity. However, beyond the ability of gold to coordinate alkynes, allenes or alkenes, gold has also proved to be extremely powerful Lewis acid triggering ring-expansion processes. This PhD work was initially aimed at the discovery of new synthetic stratergies based on the reactivity of gold with propargyl esters and strained rings.

In this thesis, we have discovered a gold-catalyzed cycloisomerization of 1- and 3-substituted cyclopropyl propargyl esters in a versatile route for the construction of 5- and 6-membered rings. In the case of 1-substituted cyclopropyl propargyl esters, a novel Au-catalyzed homo-Rautenstrauch rearrangement was achieved providing access to cyclohexenones and cyclopentenyl ketones under mild conditions. Enantiomerically enriched products were also prepared using chiral starting materials. The high degree of stereochemical configuration transfer showed in these transformations suggests that gold-stabilized nonclassical carbocations are involved as key intermediates. The interesting issue of a possible stereochemical configuration transfer in these systems was addressed both experimentally and computationally. The reaction seems to be stereospecific in the cyclization step but evidences of a process where gold-promoted cyclopropyl ring opening/epimerization/ring closure competes with the cyclization event, thus eroding the stereochemical information transfer of the process, were also obtained.

After these results, the next question was how to capitalize on the non-classical gold-stabilized carbocations for the stereocontrolled synthesis of 5- and 7-membered rings. We envisioned that a reaction sequence involving propargyl esters and dienes could be orchestrated such that gold not only catalyzed the 1,2-acetoxy migration and subsequent cyclopropanation, but could also reactivate the in situ generated vinyl acetate, thereby triggering a formal homo-Cope rearrangement to give seven-membered rings in a straightforward manner. Furthermore, if alkenes are used instead of dienes, highly substituted cyclopentenyl acetates could be obtained upon cyclopropyl ring opening. The reaction favors *trans*-2,3-disubstituted cyclopentenyl acetates through a tightly bound carbocationic transition state. The formal [4+3] cycloaddition catalyzed by gold represents an attractive alternative to previously reported rhodium-catalyzed reaction both in terms of atom economy and functional group tolerance. In addition, this methodology has allowed a formal enantioselective synthesis of the marine sesquiterpenoids frondosins A and B.

To finish, we conducted an investigation on the role of gold as a Lewis acid for the activation of cyclopropyl conjugated alkynes toward nucleophilic additions. *Trans*-alkenyl gold complexes have been proposed as intermediates in the nucleophilic attack of the gold-activated π-alkyne complexes. We decided to investigate this concept more in depth using indole derivatives in the presence of stabilized alkynyl cyclopropyl rings for the synthesis of highly substituted tetrahydrocarbazoles. The regioselectivity of the process is remarkable for *N*-protected indoles. However, the process seems to be no regioselective for non-protected ones. Remarkably, the reaction in presence of stoichiometric amounts of base improves considerable the regioselectivity of this transformation. A detailed mechanistic study focused on elucidating each individual step along the process was carried out. The formation of tetrahydrocarbazoles can be explained via gold-catalysis or via combination of both gold and acid catalysis. A desirable extension of this chemistry involves the development of asymmetric catalysis by using chiral ligands on gold or by introducing chirality in the starting materials.

Curriculum Vitae

Surname	GARAYALDE HERNANDEZ
Name	DAVID
Date of birth	April 19, 1979
Nationality	Spain

Education

2008-present **PhD in Organic Chemistry, University of Zürich, Switzerland**

PhD thesis entitled: "*Gold-catalyzed ring expansions of stabilized cyclopropyl rings"*

2006-2008 **Master in Organic Chemistry, Autónoma University, Madrid, Spain**

- **1st year topic: "The Chemistry as a Multidisciplinary Science"**
- **2nd year led to a thesis entitled:** "*Synthetic approach to Tetrodotoxin's core"*

2005-2006 **Undergraduate research**

"Synthesis of cryptates based on the N, C-pyrazolyl-pyridine motif"

2000-2005 **Bachelor in Chemistry, Autónoma University, Madrid, Spain**

Publications

1. "*Gold-Containing and Gold-Generated 1,n-Dipoles as Useful Platforms toward Cycloadditions and Cyclizations"* D. Garayalde, C. Nevado* *ACS Catal.* **2012**, *2*, 1462-1479.

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Poster Presentation/Conferences

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Poster: *"Gold-Catalyzed Cyclopenta- and Cycloheptannulation Cascades: A Stereocontrolled Approach to the Scaffold of Frondosins A and B"* D. Garayalde, and C. Nevado

July 2011 **OMCOS 16th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis, Shanghai, China**

Poster: "*Gold-Catalyzed Cyclopenta- and Cycloheptannulation Cascades: A Stereocontrolled Approach to the Scaffold of Frondosins A and B"* D. Garayalde and C. Nevado

Nov. 2010 **TokyoTech Symposium 2010, ETH-Zürich**

Lecture: *"Gold-Catalyzed Synthesis of Small Molecules"* D. Garayalde, and C. Nevado

Nov. 2010 **5th Dorothy Crowdfoot Hodgkin Interdisciplinary Symposium, UZH-Zürich**

Poster: *"On The Nature of Gold-Stabilized Non-Classical Carbocations"* D. Garayalde, and C. Nevado

July 2009 **10th Tetrahedron Symposium, Paris, France**

Poster: *"Gold-Catalyzed Cycloisomerization of Cyclopropyl Alkynyl Acetates"* D. Garayalde, X. Huang, Q. Wang, C. Nevado and A. Goeke.

2005 **COST Chemistry, Action D18. Workshop On "Lanthanide In Diagnosis and Therapy" Colonia, Germany**

Poster: *"Lanthanide complexes of new polyaminocarboxylate ligands with two chromophores derived from bispyrazolylpyridine and aceto or benzophenone: synthesis, characterization and photophysical properties"*

2005 **Advances in Supramolecular Chemistry, Strasburg, France**

Poster: *"Direct Synthesis of New Cryptates based in the N, C-Pyrazolylpyridine Motif"*

Awards

- Teaching Experience Fellowship, Autónoma University, Madrid, Spain (Feb-May 2005 and Fev-May 2006)
- 2011 SCNAT/SCS Chemistry Travel Award for participation at the OMCOS 16th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis, Shanghai, China
- Syngenta Workshop for talented PhD chemistry students, Sep. 2011